Supplementary Materials

This Supplement has been provided by the authors to give readers additional information about their work.

Supplement for:

Amyloid-Related Imaging Abnormalities in Clinical Trials of Gantenerumab in Early Alzheimer Disease

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*Please note that while this protocol states v2, this is the first implemented version of the protocol and therefore counts as the original protocol.

PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY, AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH *EARLY (*PRODROMAL TO MILD*)* ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN29922
VERSION NUMBER:	2
EUDRACT NUMBER:	2017-001364-38
IND NUMBER:	102,266
TEST PRODUCT:	Gantenerumab (RO4909832)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 21 July 2017
DATE AMENDED:	Version 2: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	11-Feb-2018 21:55:48

PROTOCOL AMENDMENT, VERSION 2: RATIONALE

Protocol WN29922 has been amended to present the results of the relative bioavailability study (WP40052) and to adjust the dosing regimen of Study WN29922 according to these results. In addition, the entry criteria of the study population have been reviewed to increase the homogeneity of the study population and to better target the right population (early Alzheimer's).

The changes below, along with a rationale for each, have been updated as follows:

- Data from the World Health Organization on Alzheimer's disease has been updated (Section 1.1).
- Safety and efficacy data from open-label extension (OLE) WN25203 and WN28745 studies have been updated. Figure 4 (OLE Results 6–9 Months at High Dose) has been added; subsequent figures have been renumbered accordingly (Sections 1.2.2, 1.2.2.3, 1.2.2.4, 1.2.3, 1.3.1, 1.3.2, 1.3.5).
- Language in the clinical studies section has been updated to reflect recent information from the relative bioavailability study (WP40052) (Section 1.2.2.5).
- The dosing regimen has been adjusted to reflect the results of the relative bioavailability study WP40052 (Sections 1.3.2, 1.3.3, 1.3.5, 3.3.1, 3.3.3, 3.3.4, 4.3.1.1, and 4.3.2.1, and Table 1, Figure 6, and Appendix 1).
- The key secondary designation has been removed; consequently the hierarchization of the secondary endpoints has also been removed. Section 3.3.7 has been deleted; subsequent sections have been renumbered accordingly (Sections 2 and 6.4.2).
- The Coding (also called Digit Symbol Substitution Test) has been added to the secondary endpoints to have a broader range of cognitive domains assessed (Sections 2, 4.5.5.1, 4.5.5.6, 4.6.2, 4.6.5, 4.6.6, and Appendix 1). Section 4.5.5.6 has been added and subsequent sections have been renumbered accordingly.
- Language has been updated to reflect changes in the study design, including China extension enrollment and analyses (Sections 3.1.1, 3.2, 3.3.1, 4.1, 4.2, 6, 6.1, and 6.8).
- For operational reasons, the Mini-Mental State Examination has been added to the optional prescreening, and the screening period has been extended by 4 weeks (Sections 3.1.1, 3.2, and 4.6.1 and Appendix 1).
- Inclusion and exclusion criteria have been updated to clarify the criteria and to further improve the safety and data quality (Sections 4.1.1, 4.1.2.1, 4.1.2.3, 4.1.2.6, and 4.1.2.7).
- With respect to blinding, the roles of the study personnel have been refined to clarify and improve the blinding (Sections 4.3.2.1 and 4.5.5.1).

- Wording around the regulatory status of the amyloid positron emission tomography (PET) tracers has been added (Section 4.3.2.2) and the PET tracer safety reporting process has been clarified (Sections 5.3.1 and 5.4.2.1).
- It has been clarified that benzodiazepine used to treat a mood or anxiety disorder as maintenance treatment is not permitted medication (Section 4.4.1).
- Cognitive, functional, and health economics assessments have been clarified to include descriptive categories, recall periods, and total score ranges as appropriate (Sections 4.5.5.1, 4.5.5.8, 4.5.5.9, 4.5.5.10, and 4.5.5.13).
- A biomarker serum sample has been added at screening and subsequent visits to allow additional analyses (Section 4.5.6.2 and Appendix 1).
- Patient non-compliance rules have been adapted to be applicable to every 4-week and every 2-week dosing regimens (Section 4.7.2).
- Reporting requirements for medical device complaints have been included (Sections 5.3 and 5.4.4).
- Reporting of serious adverse events and adverse events of special interest has been modified to be until the patient's last visit (including long-term follow-up visits) (Section 5.3.1 and 5.4.2.2). As a result, Section 5.6 "Adverse Events That Occur after the Adverse Event Reporting Period" has been deleted and subsequent sections have been renumbered.
- It has been clarified that sites are not expected to review the clinical outcome assessment data for adverse events (Section 5.3.5.14).
- Language has been changed for clarity and consistency regarding reporting of injection-site reactions (Section 5.3.5.2).
- Medical monitor information has been updated to reflect a change in the Medical Monitor (Section 5.4.1).
- The determination of sample size and an increase in sample size have been clarified (Section 6.1).
- The ARIA model has been updated (Section 3.3 and Appendix 5; Table 8, Table 9, and Figures 8–10 have been added to Appendix 5).
- To summarize the list of the prohibited medications, a table has been added as Appendix 7.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY, AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH *EARLY* (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN29922
VERSION NUMBER:	2
EUDRACT NUMBER:	2017-001364-38
IND NUMBER:	102,266
TEST PRODUCT:	Gantenerumab (RO4909832)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return the signed original of this form to the Sponsor or its designee. Please retain a signed copy of the form for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY, AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH *EARLY* (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**
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VERSION NUMBER:	2
EUDRACT NUMBER:	2017-001364-38
IND NUMBER:	102,266
TEST PRODUCT:	Gantenerumab (RO4909832)
PHASE:	Phase III
INDICATION:	Alzheimer's disease
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy and safety of gantenerumab compared with placebo in patients with *early* (prodromal to mild) *Alzheimer's disease* (AD). Specific objectives and corresponding endpoints for the study are outlined below.

Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of gantenerumab administered by SC injection compared with placebo	• The change from baseline (Day 1) to Week 104 in global outcome, as measured by the CDR-SOB
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo on cognition and function	The change from baseline to Week 104 in cognition and/or function, as measured by: • MMSE total score • ADAS-*Cog11 and* ADAS-Cog13 • Verbal Fluency Task • *Coding* • FAQ • ADCS-ADL total score *and instrumental score*
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo	The change from baseline to Week 104 in the following: • Time to clinically evident decline, defined as an increase of ≥2.0 in CDR-SOB subscore or ≥1 in at least four items of the FAQ • *Severity*, as assessed by the CDR Global Score • Function, as assessed by the CDR function subscore • Dependence level, as derived from the ADCS-ADL score • Cognition, as measured by the CDR cognition subscore • Health-related quality of life, as assessed by the QoL-AD scale • Behavioral and *neuropsychiatric* symptoms of AD, as measured by the NPI-Q • Study partner burden, as assessed by the ZCI-AD scale • Elements of resource utilization, as assessed by the RUD-Lite • Health outcomes in patient and study partner, as measured by EQ-5D questionnaire

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

Objectives and Corresponding Endpoints (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of gantenerumab compared with placebo	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Presence of ADAs during the study relative to the presence of ADAs at baseline
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the PK profile of gantenerumab	• Plasma concentration of gantenerumab (administered subcutaneously) at specified timepoints
Pharmacodynamic Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo in patients with *early* (prodromal to mild) Alzheimer's disease	• Change from baseline in brain amyloid load, as measured by amyloid PET scan in a subset of patients • Change from baseline in brain tau load, as measured by tau PET scan in a subset of patients • Change from baseline in cerebral spinal fluid markers of disease in a subset of patients, including, but not limited to, $A\beta_{1-42}$, total tau, and phosphorylated tau • MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all patients
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo in patients with *early* (prodromal to mild) Alzheimer's disease	Plasma pharmacodynamic biomarkers Change from baseline to Week 104 in functional brain connectivity, as measured by resting-state functional MRI (where available) Change from baseline to Week 104 in *integrity of white matter*, as measured by DTI-MRI (where available)

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

Study Design

Description of Study

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of gantenerumab in patients with *early (*prodromal to mild*)* AD.

The planned number of patients for the global enrollment phase for the study is approximately *760* patients: randomized in a 1:1 ratio to receive gantenerumab and placebo (*380* patients randomized to gantenerumab and *380* randomized to placebo). To maintain a balanced number of patients enrolled in each treatment arm and to ensure that the arms are comparable, randomization will be stratified by stage of disease (prodromal AD vs. mild AD), apolipoprotein E (*APOE)* allele status (presence vs. absence of the ε4 allele), use of AD medication (presence vs. absent), geographic region *(Western Europe vs. Rest of the World vs. North America)* and participation in longitudinal amyloid *and tau* positron emission tomography (PET) *substudies*. Approximately *175* centers in approximately *15* countries worldwide will participate in this study.

Patients will be selected on the basis of clinical diagnosis of probable AD (according to the National Institute on Aging/Alzheimer's Association [NIA/AA] diagnostic criteria and guidelines for AD) or prodromal AD (according to the NIA/AA diagnostic criteria and guidelines for mild cognitive impairment (MCI) due to AD). *The aim of the study is to recruit approximately 50% of the participants with prodromal AD.*

Eligible patients will be 50–90 years old, inclusive, must show evidence of β-amyloid pathology as indicated by the cerebral spinal fluid (CSF) tau to $A\beta_{42}$ ratio (CSF-enrolled patients) or positive amyloid PET scan by visual read (PET-enrolled patients), and meet eligibility criteria.

The study will consist of a screening period of up to *12* weeks in length following the signing of informed consent. *Sites also have* the option to prescreen patients on the Free and Cued Selective Reminding Test (FCSRT) *and Mini-Mental State Examination (MMSE).* Patients must sign a separate Informed Consent Form before administration of *these tests* if used for prescreening. If the results confirm a patient's eligibility, then the FCSRT *and MMSE* will not have to be completed again during the screening period as long as the test has been done within 12 weeks prior the baseline.

Eligible patients will then undergo baseline visit assessments (Day 1) prior to receiving the first dose of blinded study drug (gantenerumab or placebo). Patients will continue in the double-blind treatment period for 104 weeks. Visits and study drug administration will occur every 4 weeks (Q4W) until patients reach the *target dose*, which will be *510* mg every 2 weeks (Q2W). After the last dose of study drug (Week 102), final efficacy and safety assessments will be performed 2 weeks later (Week 104). Patients may then enroll in a*n* open-label extension (OLE) study *if eligible*. Patients who do not enter the OLE study will have additional follow-up visits at 14 and 50 weeks after the last dose for safety and limited efficacy assessments (Weeks 116 and 152, respectively). *Patients who prematurely discontinue treatment will continue in the double-blind treatment period and will be asked to return for collection of safety and limited efficacy data.*

Patients will undergo brain magnetic resonance imaging (MRI) examinations for safety monitoring and longitudinal changes in brain structure. MRI scans will be read by a central MRI reader. Patients will also undergo standard tests to monitor safety (blood tests, ECG), as well as the Columbia–Suicide Severity Rating Scale (C-SSRS) to monitor for suicidality, tests for cognition, function, and quality-of-life (QoL) status. Blood samples for the assessment of pharmacokinetic (PK) samples, pharmacodynamic (PD) biomarkers, and anti-drug antibodies will be obtained from all patients.

The incidence and nature of adverse events, serious adverse events, amyloid-related imaging abnormalities–edema/effusion (ARIA-E) and ARIA–hemosiderin deposition (ARIA-H), adverse events of special interest, ECGs, and laboratory abnormalities will be assessed on a regular basis by an unblinded independent Data Monitoring Committee (iDMC).

The study consists of three distinct periods:

- Screening *(including an optional prescreening)*: The screening period may last up to *12* weeks for each eligible patient.
- Double-blind treatment period: After screening, patients who meet all eligibility criteria will be randomly assigned to one of two arms (gantenerumab or placebo) in a 1:1 ratio. Following baseline assessments, each patient will receive a minimum of nine SC Q4W administrations of study drug (uptitration period), followed by up to 34 SC Q2W administrations of study drug in the 104-week, double-blind treatment period. The last dose of study drug will be administered at Week 102. At the end of the double-blind treatment period, all participants will undergo a Week 104 visit in order to collect data for the primary analyses.
- Post–double-blind treatment period: After the Week 104 visit, patients will be asked to come back for the long-term follow-up visits or to continue in the OLE.

  Long-term follow-up: Long-term follow-up will consist of a 50-week follow-up period with evaluations at Weeks 14 and 50 after completion of study drug administration or early termination for patients who do not enter the OLE.

  OLE study: All eligible patients will have the opportunity to enter an OLE study (details will be provided in a separate protocol).

China Enrollment Plan

Based on historical data, patient recruitment are expected to take longer in China; therefore, a specific China enrollment plan has been established. Thus, if at least 1 patient is enrolled *at sites* in *mainland* China*, Hong Kong, and Taiwan that are recognized by the China Food and Drug Administration (CFDA)* during the global enrollment phase, additional patients may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. All patients enrolled *at CFDA-recognized sites* in the global enrollment *phase* will be included in the primary analysis.

Substudies

The substudies associated with Study WN29922 will be described in separate protocols, and patients consenting to enroll in these substudies will be asked to sign the associated Informed Consent Forms.

Data Monitoring Committee

The iDMC will evaluate patient safety and efficacy on a regular basis. In addition to the data defined in the iDMC Charter (e.g., the incidence and nature of adverse events, serious adverse events, and adverse events of special interest, ARIA-E and ARIA-H), the iDMC will review all necessary cumulative data at regular intervals during the study, including efficacy when needed. It is anticipated that these assessments will occur approximately every 3 months. At the time of each review, the iDMC will make appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, the treatment regimen should be modified, the protocol should be amended, enrollment should be held pending further safety evaluations). The iDMC will also evaluate planned *or unplanned* interim analyses for efficacy or futility.

Decisions will be made in consideration of the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities will be detailed in the iDMC Charter.

Final decisions will rest with the Sponsor.

Number of Patients

The planned enrollment specifies approximately *760* patients.

Target Population

This study will enroll approximately *760* patients with increased brain amyloid burden (defined according to CSF or PET criteria), objective memory impairment indicated by cognitive assessment, and a diagnosis of probable AD or prodromal AD based on relevant NIA/AA criteria during the global enrollment phase.

An increase in sample size may be considered in the event of changes to the sample size assumptions on the basis of blinded data review or factors external to the study.

If at least 1 patient is enrolled *at sites* in *mainland* China*, Hong Kong, and Taiwan that are recognized by the CFDA* during the global enrollment phase, additional patients may be enrolled in a China extension to ensure a *total enrollment that is* sufficient *to support* registration in China. All patients enrolled *at CFDA-recognized sites* in the global enrollment phase will be included in the primary analysis.

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Ability to provide written consent signed by the patient (co-signed by the patient's legally authorized representative, if required by the local regulations, guidelines, and independent Ethics Committee or Institutional Review Board)
- Age 50–90 years old at screening, inclusive
- Availability of a person (referred to as the "study partner" throughout this protocol) who:
  - *Agrees to participate throughout the 2 years duration of study*
  - *In the investigator's judgment,* has frequent and sufficient contact (e.g., 5 times per week or approximately 10 hours per week) with the patient
  - *In the investigator's judgment, is* able to provide accurate information regarding the patient's cognitive and functional abilities, *including knowledge about domestic activities, hobbies, routines, social skills, and basic activities of daily life; work and educational history; cognitive performance including memory abilities, language abilities, temporal and spatial orientation, judgment and problem solving; emotional and psychological state; and can report any changes in the general health status*
  - Agrees to provide information *and to complete all aspects of the study* at clinic visits (which require partner input for scale completion)
  - Signs the necessary Informed Consent Form(s), and has sufficient cognitive capacity to accurately report on the patient's behavior *as well as* cognitive and functional abilities
  - Is *fluent* in *the language used at the site and has* sufficiently good general health to have a high likelihood of maintaining the same level of interaction with the patient and participation in study procedures throughout the duration of the study

    Every effort should be made to have same study partner participate throughout the duration of the study.
- Fluency in the language of the tests used at the study site
- Willingness and ability to complete all aspects of the study (including MRI, lumbar puncture [if applicable], clinical genotyping, and PET imaging [if applicable])

  The patient should be capable of completing assessments either alone or with the help of the study partner.
- Adequate visual and auditory acuity, in the investigator's judgment, sufficient to perform the neuropsychological testing (eye glasses and hearing aids are permitted)
- Evidence of AD pathological process, as confirmed by CSF tau/$A\beta_{42}$ or on amyloid PET scan by qualitative read by the core/central PET laboratory
- Demonstrated abnormal memory function at screening (FCSRT cueing index ≤ 0.67 and free recall ≤ 27)
- Screening MMSE score ≥ 22 and CDR-GS of 0.5 or 1.0

- Probable AD dementia (consistent with NIA/AA core clinical criteria for probable AD dementia) or prodromal AD (consistent with the NIA/AA diagnostic criteria and guidelines for mild cognitive decline due to AD)
- If the patient is receiving symptomatic AD medications, a stable dosing regimen for at least 3 months prior to baseline and until randomization
- Agreement not to donate blood or blood products for transfusion for the duration of the study and for 1 year after final dose of study drug
- Agreement not to participate in other research studies for the duration of this trial and its associated substudies
- For enrollment in the China extension, *patients must have residence in mainland China, Hong Kong, or Taiwan and be of Chinese ancestry.*
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least *16* weeks after the last dose of study drug

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

Exclusions Related to Central Nervous System Disorders

Patients who meet any of the following criteria related to central nervous system (CNS) disorders will be excluded from study entry:

- Any evidence of a condition other than AD that may affect cognition, including, but not limited to, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, *Parkinson* disease, corticobasal *syndrome*, Creutzfeldt-Jakob disease, progressive supranuclear palsy, frontotemporal *lobar* degeneration, Huntington disease, normal pressure hydrocephalus, seizure disorder, delirium or hypoxia
- History or presence of clinically evident *systemic* vascular disease (e.g., clinically significant carotid/vertebral *artery* stenosis or plaque, aortic aneurysm*),* that in the opinion of the investigator has the potential to affect cognitive function
- *History or presence of clinically evident cerebrovascular disease (e.g., intracranial or cerebral vascular malformations, aneurysm, intracranial macrohemorrhage)*

  Patients with asymptomatic developmental venous anomalies may be eligible after discussion with and approval by the Medical Monitor.
- *History or presence of posterior reversible encephalopathy syndrome*
- History or presence of any stroke with clinical symptoms within the past 12 months, or documented history within the last 6 months of an acute event that is consistent, in the opinion of the investigator, with a transient ischemic attack
- History of severe, clinically significant (persistent neurologic deficit or structural brain damage) CNS trauma (e.g., cerebral contusion)
- History or presence of intracranial mass (e.g., glioma, meningioma) that could potentially impair cognition

- Presence of infections that affect brain function or history of infections that resulted in neurologic sequelae (e.g., HIV, syphilis, neuroborreliosis, and viral or bacterial meningitis and encephalitis)
- History or presence of systemic autoimmune disorders that potentially cause progressive neurologic disease with associated cognitive deficits (e.g., multiple sclerosis, lupus erythematosus, anti–phospholipid antibody syndrome, and Behçet disease)
- History of schizophrenia, schizoaffective disorder, major depression, or bipolar disorder

  History of major depression is acceptable if patient has had no episode within the past year or is considered in remission or depression is controlled by treatment.
- At risk *for* suicide in the opinion of the investigator
- Alcohol and/or substance abuse or dependence (according to the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, Version 5) within the past 2 years

  Nicotine use is allowed.

  Marijuana use is not allowed and must be discontinued at least 3 months before screening.

Imaging-Related Criteria

Patients who meet any of the following imaging criteria will be excluded from study entry:

- According to the MRI central reader, MRI evidence of any of the following:
  - $>$ 2 lacunar infarcts
  - Any territorial infarct $>$ 1 cm^3
  - Any white matter lesion that corresponds to an overall Fazekas score of 3 that requires at least one confluent hyperintense lesion on the fluid-attenuated inversion recovery (FLAIR) sequence, which is $\geq$ 20 mm in any dimension
- Combined number of microbleeds and areas of leptomeningeal hemosiderosis (i.e., cumulative ARIA-H) on MRI more than five (and should not include any disseminated leptomeningeal hemosiderosis) based on the review performed by the central reader prior to randomization
- Presence of any other significant cerebral abnormalities, including ARIA-E, as assessed on MRI
- Inability to tolerate MRI procedures or contraindication to MRI, including, but not limited to, presence of pacemakers not compatible with MRI, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan, or any other clinical history or examination finding that, in the judgment of the investigator, would pose a potential hazard in combination with MRI

Cardiovascular Disorders

Patients who meet any of the following criteria related to cardiovascular disorders will be excluded from study entry:

- History or presence of clinically symptomatic atrial fibrillation requiring maintenance therapy

  Patients who experienced non-valvular atrial fibrillation that resolved more than 1 year ago and was not associated with prior stroke are eligible.
- Within the last year, unstable or clinically significant cardiovascular disease (e.g., myocardial infarction)

  *H*eart failure classified as New York Heart Association Class *I* or *II* cardiac disease *is allowed if not associated with hospitalization within the previous 12 months.*
- Uncontrolled hypertension (e.g., blood pressure generally $>$ 160 mmHg systolic or $>$ 95 mmHg diastolic)

Hepatic and Renal Disorders

Patients who meet any of the following criteria related to hepatic and renal disorders will be excluded from study entry:

- Chronic kidney disease, indicated by creatinine clearance $<$30 mL/min to be calculated by the central laboratory using the Cockcroft-Gault formula at screening, which remains $<$30 mL/min if retested
- Confirmed and unexplained impaired hepatic function as indicated by screening AST or ALT $\geq 3\times$ the upper limit of normal (ULN) or total bilirubin $\geq 2\times$ ULN

Infections and Immune Disorders

Patients who meet any of the following criteria related to infections and immune disorders will be excluded from study entry:

- History of, or known to currently have HIV infection, or hepatitis B or hepatitis C infection that has not been adequately treated in the opinion of the investigator, or history of spirochete infection of the CNS (e.g., syphilis, Lyme disease, or borreliosis)
- Systemically, clinically significantly immunocompromised patients, owing to continuing effects of immune-suppressing medication

Metabolic and Endocrine Disorders

Patients who meet any of the following criteria related to metabolic and endocrine disorders will be excluded from study entry:

- Abnormal thyroid function as indicated by abnormal screening tests that are judged to be clinically significant by the investigator, or abnormal thyroid function that requires a new treatment or an adjustment of current treatment

  A patient may be rescreened if there is no improvement in cognition in the investigator's judgment after 3 months of adequate treatment for thyroid function.
- *Patients with evidence of folic acid deficiency (as indicated by folic acid level below the lower limit of normal) or vitamin B-12 deficiency (as indicated by vitamin B-12 level below the lower limit of normal and/or methylmalonic acid levels above ULN)*

  A patient may be rescreened if there is no improvement in cognition after 3 months of adequate treatment for folic acid or vitamin B-12 deficiency.
- Screening hemoglobin A_{1c} (HbA_{1C}) $>$8% (retesting is permitted if slightly elevated) or poorly controlled insulin-dependent diabetes (including hypoglycemic episodes)

  A patient may be rescreened after 3 months to allow optimization of diabetic control.

Exclusions Related to Medications

The following medications are prohibited for a pre-specified duration prior to study start, as indicated, and during the entire period of study participation (Patients who start these medications during the study may be withdrawn from study treatment):

- Any previous administration of gantenerumab or active immunotherapy (vaccine) that is being evaluated to prevent or postpone cognitive decline
- Any passive immunotherapy (immunoglobulin) or other long–acting biologic agent that is under evaluation to prevent or postpone cognitive decline within 1 year of screening
- Any other investigational treatment or any other treatment with a monoclonal antibody within 5 half-lives or 4 months prior to screening, whichever is longer
- Any previous treatment with medications specifically intended to treat Parkinson symptoms or any other neurodegenerative disorder within 1 year of screening and with no *plans to initiate such medications* prior to randomization

  Certain medications are acceptable if the patient is taking the medicine for a non-neurodegenerative disorder, such as restless leg disorder (e.g., pramipexole).

- Typical antipsychotic or neuroleptic medication within 6 months of screening and with no planned changes prior to randomization except as brief treatment for a non-psychiatric indication (e.g., emesis)

  Atypical antipsychotic medications are not allowed except for intermittent short-term use and will need to be discontinued 2 days or *at least* 5 half-lives (whichever is longer) prior to any neurocognitive assessment.
- Anti-coagulation medications within 3 months of screening with no *plans to initiate any* prior *to* randomization

  Anti-platelet treatments (e.g., aspirin, clopidogrel, and dipyridamol) are permitted.

  Short-term, perioperative use of anticoagulant medications will not result in permanent discontinuation from the study; however, any such use must be discussed prospectively with the Medical Monitor and may require temporary study drug interruption.
- Chronic use of opiates or opioids (including long-acting opioid medication) within 3 months of screening with no *plans to initiate any* prior *to* randomization

  Intermittent short-term use of short–acting opioid medications for pain is permitted except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.
- Stimulant medications (amphetamine, methylphenidate preparations, or modafinil) within 1 month of screening and throughout the study
- Chronic use of benzodiazepines, barbiturates, or hypnotics from 3 months before screening and with no *plans to initiate any* prior *to* randomization

  Intermittent short-term use of benzodiazepines, buspirone, or short-acting hypnotic medication for sleep or anxiety is allowed except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

Other Exclusions

Patients who meet any of the following criteria will be excluded from study entry:

- Other causes of intellectual disability that may account for cognitive deficits observed at screening (e.g., static encephalopathy, closed brain injury, mental retardation)

  This may be based on, for example, patient's sufficient education or work experience.
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study
- Deformity of the lumbosacral region of the spine that in the opinion of the investigator would contraindicate lumbar puncture in patients who will have lumbar puncture
- Clinically significant abnormal screening blood, CSF (if applicable), or urine results that remain abnormal at retest
- Impaired coagulation (screening prothrombin time [PT] $> 1.2 \times$ the ULN that remains abnormal on retest)
- History of cancer, with the following exceptions:
  - If considered to be cured
  - If not being actively treated with anti-cancer therapy or radiotherapy and, in the opinion of the investigator, is not likely to require treatment in the ensuing 5 years
  - For prostate cancer or basal cell carcinoma, no significant progression over the previous 2 years
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins, including gantenerumab
- Hypersensitivity to any of gantenerumab excipients
- Any other severe or unstable medical condition that, in the opinion of the investigator or Sponsor, could be expected to progress, recur, or change to such an extent that it could put the patient at special risk, bias the assessment of the clinical or mental status of the patient to a significant degree, interfere with the patient's ability to complete the study assessments, or would require the equivalent of institutional or hospital care

- Residence in a skilled nursing facility such as a convalescent home or long-term care facility: Patients who subsequently require residence in such facilities during the study may continue in the study and be followed for efficacy and safety, provided that they have a study partner who meets the minimum requirement

End of Study

The end of the study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for safety analyses or safety follow-up is received for the last patient, whichever occurs later.

Length of Study

The study will consist of a screening period of up to 12 weeks (including the optional prescreening period) for each eligible patient who signs the Informed Consent Form and agrees to participate, followed by a double-blind treatment period of 102 weeks of study drug treatment plus a visit 2 weeks after the last dose (Week 104), and followed by the post–double-blind treatment period of two follow-up visits at 14 and 50 weeks after the last dose (Weeks 116 and 152, respectively). Thus, for a patient not entering the OLE, the maximum length of study is approximately 164 weeks.

Investigational Medicinal Products

The investigational medicinal product for this study is gantenerumab.

Test Product (Investigational Drug)

Gantenerumab or placebo will be administered by SC injection to all patients.

Gantenerumab will be administered by SC injection to all patients randomized to the active treatment arm, regardless of *APOE* ε4 status, at a dose of 120 mg SC Q4W for 3 months, 255 mg SC Q4W for 3 months, and 510 mg SC Q4W for 3 months, prior to reaching the target dose. Once the target dose is reached, study drug will be administered every 2 weeks (Q2W administration of 510 mg SC gantenerumab). The switch to a Q2W administration schedule allows decreasing the number of SC administrations in the abdomen per visit.

For Q4W injections, a time window of ±7 days is allowed for dosing visits. Once study drug is administered Q2W, the time window for dosing visits is ±3 days.

Regardless of dose, each patient will undergo up to a total of 43 dosing visits in the study. Injections will be administered as one 0.8-mL (120-mg dose), one 1.7-mL (255-mg dose), or two 1.7-mL injections (510-mg dose) subcutaneously to the abdomen, respectively.

Placebo of identical composition (except protein) and identical volume to gantenerumab will be administered by SC injection to all patients randomized to placebo at the same frequency and using the same route of administration.

On study drug administration days that include efficacy assessments, study drug must be administered at the clinical site. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

At applicable sites, study drug may be administered by a trained nursing professional at the patient's home or another suitable location, if the patient has given written informed consent to participate in home nursing visits.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

PET Tracers

All patients who are enrolled in PET substudies will be assessed by PET imaging using an appropriate PET ligand. For screening, the possible amyloid PET ligands will be florbetapir, florbetaben, and flutemetamol. *According to E.U. guidance, the PET tracers used in the context of this study have been designated as non-IMP. In some regions, according to local regulations, these PET tracers may be considered to be IMP.*

In countries where the PET radioligands are approved for marketing, the approved local product information will be provided, and in countries where they are not approved for marketing, the Investigator's Brochures will be provided.

Details about the PET substudies are described in separate protocols.

Statistical Methods

Primary Analysis

The primary efficacy outcome measure is the change in CDR-SOB from baseline (Day 1) to Week 104. For the primary outcome measure, the difference in mean change from baseline to Week 104 between gantenerumab-treated patients and placebo-treated patients will be estimated. The analysis will use the ITT population, with patients grouped according to the treatment assigned at randomization. A mixed model repeated measures (MMRMs) analysis adjusting for baseline CDR-SOB score, disease stage, *APOE* ε4 status, geographic region and use of AD medication at baseline will be used to estimate the mean change from baseline to Week 104 for the primary endpoint.

The model will include the change from baseline in CDR-SOB as the dependent variable. The effects in the model will include baseline CDR-SOB score, disease stage, *APOE* ε4 status, geographic region, use of AD medication at baseline, treatment group, visit, and treatment-by-visit interaction. Visit week will be treated as the repeated variable within a patient. Disease stage, *APOE* ε4 status, geographic region, background medication at baseline, patient, treatment, and visit week will be treated as class variables. An unstructured variance-covariance structure will be applied to model the within-patient errors; in case of non-convergence, compound symmetry will be used.

The difference in the change from baseline of the patients randomized to gantenerumab from patients randomized to placebo will be estimated at each timepoint. The 95% CI and p-value for treatment difference will be presented.

All efforts will be made to minimize missing data. The Sponsor plans to request patients who discontinue early from study treatment to return for collection of safety and limited efficacy data (i.e., the primary and secondary efficacy endpoints) until Week 104. To explore the robustness of MMRM results for the primary efficacy conclusions sensitivity analyses (e.g., using multiple imputation and pattern mixture models) will be performed. Descriptive summaries of the number of patients with missing data, the timing, and reasons for discontinuation from the study will also be provided by treatment group.

Determination of Sample Size

Determination of sample size is based on patients enrolled in the global enrollment phase. In this study, approximately *760* patients will be enrolled and randomized in 1:1 ratio to each treatment arm (gantenerumab or placebo) during the global enrollment phase. A sample size increase may be considered if factors external to the study or blinded study data analysis would warrant a change to the sample size assumption.

Additional patients may be randomized during the China extension if at least 1 patient is enrolled *at sites in mainland China, Hong Kong, and Taiwan that are recognized by the CFDA* during the global enrollment phase.

The estimated sample size required to demonstrate efficacy with regard to CDR-SOB is based on the following assumptions:

- The mean change in the CDR-SOB from baseline to Week 104 is *2.5* points in the placebo arm
- A common standard deviation across treatment arms for change of approximately *2.97* from baseline to Week 104 in the CDR-SOB
- Gantenerumab has a true effect of a 30% relative reduction in deterioration of CDR-SOB

Based on these assumptions*, and using a student's T-test with equal variance,* a sample size was calculated for 80% power to detect a true treatment effect of 30% relative reduction in deterioration of CDR-SOB at a two-sided α of 0.05.

Uncertainties on parameters affecting the power (e.g., dropout rate, study drug discontinuation rate, standard deviation, and placebo decline) were assumed to be equivalent to a drop-in sample size of up to around 35% and were corrected for accordingly. This calculation leads to a total of 760 patients in the study.

The sample size may be increased from *760* up to *1140* patients (*570* patients per arm). *The* decision whether to increase sample size will be based on a blinded assessment of pooled CDR-SOB change from baseline. Further details will be described in the Statistical Analysis Plan (SAP). The assessment will be performed by the Sponsor at a specified timepoint. *The sponsor will remain blinded.* The sample size will not be reduced on the basis of this assessment. Other factors external to the study may also trigger a decision to increase sample size.

Interim Analyses

Planned Interim Analysis

An interim analysis for efficacy and futility is to be conducted approximately 24 months after 50% of the targeted study enrollment has been reached.

An independent data coordinating center will be responsible for the interim analyses and study results will only be reviewed by the iDMC. The Sponsor will remain blinded.

The iDMC may recommend stop for futility if the failure criterion is met. The failure criterion will represent a low probability of a positive study outcome given the data observed at the time of interim analysis. The failure criterion will be prespecified in the iDMC SAP.

In contrast, the iDMC may "declare the study positive for overwhelming efficacy" if the study meets the success criterion on the primary endpoint. The success criterion is defined as the p-value threshold determined by standard Lan and DeMets methodology for group sequential design using the O'Brien-Fleming boundary function. If the study continues beyond the interim analysis, the critical value at the final analysis will be adjusted accordingly.

Optional Interim Analysis

Based on availability of information pertaining to gantenerumab or other compounds with similar mode of action that may emerge during the course of this study, the Sponsor may choose to conduct an additional interim analysis for futility and/or efficacy beyond the interim analysis mentioned above.

An independent data coordinating center will be responsible for the interim analyses and study results will only be reviewed by the iDMC. The Sponsor will remain blinded.

Details of the interim analyses, including the decision to conduct the optional interim analysis, the rationale, timing, and statistical details for the analyses (such as the data that would be reviewed by the iDMC and futility or efficacy thresholds) will be documented in the Statistical Analysis Plan, and the Statistical Analysis Plan will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Aβ	amyloid-beta
AD	Alzheimer's disease
ADA	anti-drug antibody
ADAS-Cog11	Alzheimer's Disease Assessment Scale–Cognition, Subscale 11
ADAS-Cog13	Alzheimer's Disease Assessment Scale–Cognition, Subscale 13
ADCS-ADL	Alzheimer's Disease Cooperative Study Group–Activities of Daily Living
ADL	activities of daily living
APOE ε4	apolipoprotein E, allele ε4
ARIA	amyloid-related imaging abnormality
ARIA-E	amyloid-related imaging abnormality–edema/effusion
ARIA-H	amyloid-related imaging abnormality–hemosiderin deposition
AUC	area under the concentration–time curve
AUC_{inf}	*area under the concentration–time curve from Time 0 to infinity*
BOLD	blood oxygenation level-dependent
BGTS	Barkhof grand total score
CDR	Clinical Dementia Rating
CDR-GS	CDR global score
CDR-SOB	Clinical Dementia Rating–Sum of Boxes
CFDA	*China Food and Drug Administration*
C_{max}	maximum concentration
COA	clinical outcome assessment
CRO	contract research organization
CSF	cerebral spinal fluid
C-SSRS	Columbia–Suicide Severity Rating Scale
CT	computed tomography
DTI	diffusion tensor imaging
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
EQ-5D	EuroQol-Five Dimensions questionnaire
FA	fractional anisotropy

Abbreviation	Definition
FAQ	Functional Activities Questionnaire
FCSRT	Free and Cued Selective Reminding Test
FCSRT-IR	Free and Cued Selective Reminding Test–Immediate Recall
FDA	(U.S.) Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
GRE	gradient recalled echo
HbA_{1C}	hemoglobin A_{1c}
HIPAA	Health Insurance Portability and Accountability Act
HN	home nursing
ICH	International Council on Harmonisation
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ISR	injection-site reaction
ITT	intent to treat
IWG	International Working Group
IV	intravenous
IxRS	interactive voice or Web-based response system
LPLV	last patient, last visit
MAD	multiple-ascending dose
MCI	mild cognitive impairment
MMRM	mixed model repeated measure
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NIA/AA	National Institute on Aging/Alzheimer's Association
NPI-Q	Neuropsychiatric Inventory–Questionnaire
OLE	open-label extension
PD	pharmacodynamic
PET	positron emission tomography
PK	pharmacokinetic
PT	prothrombin time
p-tau	phosphorylated tau
QoL	quality of life
QoL-AD	Quality of Life–Alzheimer's Disease

Abbreviation	Definition
Q2W	every 2 weeks
Q4W	every 4 weeks
RBR	Research Biosample Repository
rs-fMRI	resting-state functional magnetic resonance imaging
RUD-Lite	Resource Utilization in Dementia–Lite
SAD	single-ascending dose
SAP	Statistical Analysis Plan
SC	subcutaneous
SOB	Sum of Boxes
SUVr	standardized uptake value ratio
t-tau	total tau
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing
ZCI-AD	Zarit Caregiver Interview–Alzheimer's Disease

1. BACKGROUND

1.1 BACKGROUND ON ALZHEIMER'S DISEASE

The World Health Organization estimates that *around 50* million people worldwide are diagnosed with dementia and that there are *10* million new cases every year. The total number of people with dementia is estimated to reach *82* million in 2030 and will *more than* triple by 2050 to *152* million. Alzheimer's disease (AD) is the most common form of dementia, accounting for 60%–70% of cases (World Health Organization 2017). The prevalence of AD increases with age, with a global prevalence of 5%–8% in people 60 years and older. Because of its increasing prevalence, long duration, and high cost of care, AD is expected to continue to represent a major public health problem for decades to come.

There is great inter-individual variability in AD progression with survival dependent on many factors, including age at onset. In general, the clinical picture evolves from "predementia" or "prodromal AD" to mild, moderate, and then severe AD. At the early stage of AD, a slight impairment of memory, language, and visuospatial function can be observed. As AD advances, patients become progressively impaired and the burden on caregivers significantly increases. The median survival time following a diagnosis of AD strongly depends on the patient's age at diagnosis and ranges from 8.3 years for persons diagnosed with AD at 65 years old to 3.4 years for those 90 years old (Brookmeyer et al. 2002). On average, individuals live 3–9 years after diagnosis (Helzner et al. 2008) and some survive as long as 20 years.

It is well recognized that in comparison to other therapeutic domains, there is a real unmet medical need in AD therapy (Gauthier et al. 2016). To date, only five medications have received marketing approval to treat the symptoms of AD, including acetylcholinesterase inhibitors (AChEi) and N-methyl-d-aspartate receptor antagonists. These approved drugs are recognized to temporarily improve some clinical symptoms of AD in some patients but do not modify progression of the disease (Cummings et al. 2016). Recent efforts have mostly focused on therapies targeting amyloid (Bachurin et al. 2017) as these offer the most compelling therapeutic targets (Graham et al., 2017). These therapies are based on the amyloid hypothesis that posits amyloid-β (Aβ) accumulation as the primary factor driving Aβ pathogenesis (Selkoe 1991; Hardy and Selkoe 2002; Selkoe and Hardy 2016). This Aβ accumulation in the brain begins well before the development of clinical dementia in AD and causes a series of downstream events leading to synaptic dysfunction, inflammation, neurodegeneration, and clinical symptoms. For these reasons, treatments that prevent, slow, or decrease the accumulation of brain Aβ are being tested as therapeutic agents in AD.

Preclinical evidence has suggested that monoclonal Aβ antibodies may be able to remove and reduce deposition of Aβ aggregates from the brain. In transgenic animal models of AD, vaccination with Aβ or passive immunization with anti–Aβ antibodies resulted in decreased amyloidosis and in improvement of memory function in some

transgenic models cognitive function (Janus et al. 2000). Accumulating clinical evidence also supports that monoclonal Aβ antibodies can bind Aβ and promote its clearance (Salloway et al. 2009; Ostrowitzki et al. 2012), reduce deposition of Aβ aggregates, and reduce markers of neurodegeneration in the cerebral spinal fluid (CSF) (Roche Research Report No. 1066251). In a Phase I study, reduction of deposited amyloid as shown on brain amyloid positron emission tomography (PET) imaging was associated with a time and dose-related slowing of cognitive decline (Sevigny et al. 2016). Because the neurological changes associated with AD develop decades before clinical symptoms emerge, it is thought that earlier intervention may be more effective in arresting or delaying disease progression (Sevigny et al. 2016). Consequently, therapies targeting this process have the potential to significantly alter the progression of the disease. Gantenerumab, a fully human monoclonal antibody targeting aggregated forms of Aβ-like Aβ oligomers, fibrils, and plaques, is expected to address this need (Bohrmann et al. 2012).

1.2 BACKGROUND ON GANTENERUMAB

Gantenerumab (or RO4909832) is a fully human anti–Aβ peptide antibody developed by in vitro selection utilizing aggregated Aβ and in vitro maturation within a complete human Igγ, subclass-1 framework (IgG1). Gantenerumab recognizes a conformational epitope of Aβ present in aggregated Aβ and that is demonstrated for both major species of Aβ that is, $Aβ_{1–40}$ and $Aβ_{1–42}$. Gantenerumab has a molecular mass of 146.3 kDa. In vitro, gantenerumab recognizes synthetic aggregated Aβ fibrils and Aβ oligomers with high nanomolar affinity (K_D, ~0.6–1.2 nM). Based on additional in vitro studies and studies in animal models, the pharmacologic profile suggests that in humans gantenerumab may prevent, inhibit, and reduce accumulation of Aβ, which is believed to play an important role in the pathogenesis of AD.

Gantenerumab is manufactured by cell culture of a recombinant Chinese hamster ovary–K1 mammalian cell line and subsequent purification of the antibody. The gantenerumab drug substance manufacturing was optimized during development, leading to several manufacturing processes (G1, G2, and G3). Recently, the gantenerumab manufacturing process was further optimized from G3 to G4 to improve process robustness and increase overall process yield. *Drug material manufactured by G4 process will be used in Phase III clinical trials (e.g., Study WN29922).* Gantenerumab is in clinical development for patients with *early (*prodromal to mild*)* AD and is also being investigated in carriers of familial AD mutations (DIAN-TU) (Bateman et al. 2017).

Refer to the gantenerumab Investigator's Brochure for details on nonclinical and clinical studies.

1.2.1 Nonclinical Studies

1.2.1.1 Nonclinical Pharmacology

The binding characteristics of gantenerumab were engineered to achieve specific and highly sensitive recognition of the assembly structure of aggregated human $A\beta_{1-42}$ and $A\beta_{1-40}$ peptides, which are major components in Aβ plaques. Specificity was demonstrated ex vivo for genuine human Aβ plaques in AD brain slices. The minimum effective concentration for staining of human Aβ plaques is 10 ng/mL (0.07 nM).

Gantenerumab showed a concentration-dependent increase in cellular phagocytosis of human Aβ plaques by human primary cells like microglia and differentiated macrophages in a brain-slice phagocytosis assay. The measured minimal effective concentration of 10 ng/mL (0.07 nM) is consistent with the observed efficacy for human Aβ plaque binding.

In single-dose and multiple-dose studies, effective brain penetration and binding to Aβ plaques in vivo were demonstrated in various models of AD-related amyloidosis, such as the PS2APP transgenic mouse model. Gantenerumab showed significant and accumulative binding to Aβ plaques. The data indicate that there is no requirement for continuous high peripheral levels to achieve a sustained binding of gantenerumab to amyloid plaques.

The plaque binding of gantenerumab from several manufacturing processes has been evaluated. The degree of plaque binding for gantenerumab manufactured by the G1 and G2 processes was investigated by semi-quantitative fluorescence imaging and was comparable in a 2-week IV safety study in PS2APP transgenic mice at doses of 0, 2, 10, and 40 mg/kg every 3 days.

An additional study, which compared the plaque binding of gantenerumab from the G3 and G4 manufacturing processes following single IV administration to PS2APP transgenic mice at a dose level of 40 mg/kg and assessed by semi-quantitative fluorescence imaging after 7 days, indicated slightly increased target engagement of the G4 material consistent with observed differences in exposure (see Section 1.2.1.2).

Chronic treatment with gantenerumab showed significant efficacy by halting progression of amyloidosis in transgenic PS2APP, APP_{London}, and tau PS2APP mouse models of AD. Amyloid reduction was evident by prevention of new plaque formation and removal of preexisting amyloid plaques by engaging microglia cells.

1.2.1.2 Nonclinical Pharmacokinetics and Metabolism

The pharmacokinetics of gantenerumab were studied in mice, rats, and cynomolgus monkeys following IV administration. Gantenerumab pharmacokinetics were characterized by a rapid initial decrease in plasma levels during the first 24 hours, followed by a long half-life, ranging from 4 to 13 days in all species. Overall, the studies demonstrate that gantenerumab has pharmacokinetic (PK) properties similar to other IgGs.

The pharmacokinetics of gantenerumab were also studied following SC administration in cynomolgus monkeys and mice. In cynomolgus monkeys, maximum plasma levels were reached after 3 days. The average bioavailability was estimated at 76%.

Gantenerumab was shown to penetrate the brain in both the monkey and mouse. Brain penetration in the monkey was evident from analysis of CSF samples. The CSF to plasma ratios ranged from 0.006% to 0.018%. Penetration and binding to $A\beta_{1-42}$ plaques in the mouse brain were evident from immunostaining for gantenerumab of brain sections obtained from PS2APP mice dosed with gantenerumab.

Rat PK studies have been conducted to compare the pharmacokinetics of gantenerumab derived from different manufacturing processes (G1, G2, G3, and G4).

Following IV administration to rats, the pharmacokinetics of the G1 and G2 materials were similar. The area under the concentration–time curve (AUC) of the G2 material was slightly lower and accounted for about 80% of the of the G1 material. Although standard bioequivalence criteria for AUC were not met, the observed difference in AUC was not considered to have an impact on the use of the G2 material in further clinical development as the difference in AUC is small. The average terminal half-life of both materials was comparable (8.0 and 8.8 days for the G1 and G2 materials, respectively).

A study comparing the pharmacokinetics of gantenerumab derived from the G3 and G4 manufacturing processes showed that the AUC of G3 material (used in the ongoing Phase III open-label extension [OLE] studies WN25203 and WN28745) was lower compared with the G4 material that will be used in Study WN29922 (mean±SD: 932±196 and 1270±187 (μg• hr/mL)/(mg/kg), respectively. The average terminal half-life of both materials was similar (11.5 and 12.3 days for G3 and G4 materials, respectively).

1.2.1.3 Toxicology and Safety Pharmacology

Potential adverse effects in relation to the presence and destruction of $A\beta_{1-42}$ plaques were assessed in PS2APP transgenic mice that were treated with up to 375 mg/kg/wk of IV gantenerumab for up to 26 weeks. No evidence of inflammatory reaction in general or other adverse effects were observed in these studies. Decreases in neutrophils and protein (albumin) that were not considered adverse were seen in mice. As a compensatory response, myeloid hyperplasia in the bone marrow was inconsistently detected in some animals. The reason for the low neutrophil counts is unclear but may

be a mouse-specific effect of gantenerumab on neutrophils. Indeed, no such finding was observed in long-term nonclinical (murine and monkey) and clinical studies, and there have been no symptoms indicating immunosuppression in either species.

In cynomolgus monkeys, gantenerumab was well tolerated in repeat-dose IV toxicity studies of 13 and 26 weeks in duration (3, 10, and 20 mg/kg) and in SC toxicity studies of 13 weeks in duration (20 mg/kg) and 39 weeks in duration (up to 375 mg/kg). In the 26-week toxicity study, in which gantenerumab was administered once weekly, one male monkey in Group 2 (3 mg/kg) was found dead 24 hours after receiving the 26th dose (Day 177). The death was not considered to be related to gantenerumab treatment but rather to a bacterial infection detected on histopathology. There was no treatment-related effect on hematologic parameters (i.e., neutrophil counts) in studies in cynomolgus monkeys.

In the absence of any adverse treatment-related effect in the 39-week toxicity study, a no-observed-adverse-effect level of 375 mg/kg/wk was established, which correlated with a mean maximum concentration (C_{max}) of 2535 μg/mL (male and female animals combined) and a mean area under the concentration–time curve from Time 0 to 168 hours ($AUC_{0-168hr}$) of 386,000 μg • hr/mL (male and female animals combined).

Reproductive toxicity studies in transgenic PS2APP mice did not reveal an effect of gantenerumab on fertility, embryo–fetal, or post-natal development.

1.2.2 Clinical Studies

Gantenerumab has been investigated in *10* completed Phase I clinical studies: three single-ascending dose (SAD) studies (BN18726, JP22474, and BP30042) of healthy volunteers *and patients with mild to moderate AD*, two multiple-ascending dose (MAD) studies (NN19866 and JP22431) of patients with mild to moderate AD, and three bioavailability studies of healthy subjects (one comparing the IV and SC formulations of gantenerumab [Study WP22461], two comparing lyophilized and high-concentration liquid formulations of gantenerumab [Studies WP27951 and BP29113]). *In addition, a tolerability study comparing the pain between faster and slower SC administrations of gantenerumab has been completed (Study WP39322).*

In order to assess suitability of the G4 material for future Phase III studies, an extended analytical comparability program was conducted followed by the nonclinical studies. Since differences were observed in AUC, a human relative bioavailability study (WP40052) comparing G3 and G4 gantenerumab after SC administration *has also been* conducted.

A total of *543* subjects have participated in the Phase I studies; of these participants, *406* healthy volunteers and 101 patients with AD have received gantenerumab. Two Phase III studies designed to examine efficacy and safety of gantenerumab in patients with prodromal AD (Study WN25203) and mild AD (Study WN28745) have been

converted to OLE studies. The OLE studies examining the safety and tolerability of higher doses of gantenerumab in prodromal AD (Study WN25203) and mild AD (Study WN28745) are ongoing.

Results of relevant studies are summarized below. Refer to the Gantenerumab Investigator's Brochure for further information.

In addition, gantenerumab is being investigated in the Dominantly Inherited Alzheimer Network Trial, a Phase II/III study sponsored by the Washington University School of Medicine, examining the safety, tolerability, biomarker status, and efficacy of gantenerumab (as measured by cognition) in patients who are known to have an AD-causing mutation and are therefore at risk for developing AD dementia.

1.2.2.1 Study NN19866

In the MAD study (NN19866), a total of 60 patients (34 males and 26 females) diagnosed with mild to moderate probable AD received multiple IV doses of gantenerumab (doses ranging from 6 mg to 20 mg, 60 mg, and 200 mg) or placebo every 4 weeks (Q4W) for up to 7 months. Owing to amyloid-related imaging abnormalities (ARIAs), or ARIAs of "vasogenic edema" (ARIA-E) and of "hemosiderosis or microbleeds" (ARIA-H), on brain magnetic resonance imaging (MRI) scans that occurred in some patients after two to four doses of 200 mg of gantenerumab in Cohort 4 (200 mg IV Q4W gantenerumab [equivalent to 330 mg SC Q4W] or placebo), it was decided to terminate dosing for all patients on 9 June 2008. The findings resolved spontaneously within 1–4 months after discontinuation of gantenerumab and no patient required treatment.

1.2.2.1.1 Study NN19866: Pharmacodynamic Results in the NN19866-PET Substudy

In a positron emission tomography (PET) substudy of Study NN19866 (NN19866-PET), the effects of gantenerumab on amyloid load in the brain (defined as standardized uptake value ratio [SUVr] of a cortical composite volume of interest over mean cerebellum gray and using ^{11}C-PiB PET) were evaluated in 18 patients (4 in the placebo group, 8 in the 60-mg IV gantenerumab dose group, and 6 in the 200-mg IV gantenerumab dose group) after 6 months. A mean decrease of 14.9% from baseline was observed in the 200-mg gantenerumab dose group, while an increase was seen in the placebo group (mean, 20.9%), with relative stability compared with baseline in the 60-mg group (mean, 5.3%) (Ostrowitzki et al. 2012).

1.2.2.2 Study WN25203

Based on the results from Study NN19866 and from a relative bioavailability study WP27951, the doses of 105 mg SC Q4W (equivalent to 60 mg IV Q4W) and 225 mg SC Q4W (equivalent to 130 mg IV Q4W) were selected *for Study WN25203*.
Study WN25203 was initially designed as a Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy

of 105 mg and 225 mg of gantenerumab administered subcutaneously Q4W in prodromal AD after 2 years of treatment. Randomization was based on apolipoprotein E, allele ε4 (*APOE* ε4) status. Selection of gantenerumab doses was largely driven with the objective of reducing risk of MRI findings (in the context of the clinical understanding of ARIAs at the time of study design) and by pharmacodynamic (PD) results in the MAD study NN19866. Study WN25203 enrolled 799 patients, and 797 patients were treated (the safety-evaluable population). Following a planned interim futility analysis when approximately 50% of patients had completed 2 years of treatment), the study was declared futile and dosing with the originally selected doses (105 mg and 225 mg) was suspended in December 2014. The mean duration of double-blind treatment was 1.73 years.

Safety analyses confirmed ARIAs and injection-site reactions (ISRs) (associated with SC administration) as identified risks of gantenerumab (see Section 1.2.3 for more details). Approximately 90% of patients experienced at least one adverse event, with the incidence comparable between treatment arms. The incidence of serious adverse events was 19.5%, 17.3%, and 16.9% in the placebo, 105-mg gantenerumab, and 225-mg gantenerumab groups, respectively *(Ostrowitzki et al. 2017)*.

Subsequently, the trial has been converted into an OLE study evaluating doses of up to 1200 mg (see Section 1.3.1).

1.2.2.3 Study WN28745

Study WN28745 was initially designed as a Phase III, 2-year, double-blind, placebo-controlled, efficacy, and safety study of gantenerumab in approximately 1000 patients with mild AD. Patients randomized to receive gantenerumab were to follow a slow titration scheme independent of *APOE*-ε4 genotype, starting at 105 mg of SC gantenerumab Q4W for the first 24 weeks, with progression to 225 mg, based on acceptable results of the control MRI scan. The study enrolled 389 patients, *and 387 patients were treated. There were 108 patients also enrolled in a PET substudy of brain amyloid imaging (Study WN28745-PET).* Following the WN25203 futility analysis, study recruitment was stopped and the study was converted to an OLE study, evaluating the safety and tolerability of gantenerumab at higher doses (up to 1200 mg).

1.2.2.4 OLE Studies WN25203 and WN28745

Additional analyses of Study WN25203 results indicated that higher doses of gantenerumab may achieve clinically relevant effects on cognition and function (see Section 1.3.1). Thus, both Studies WN25203 and WN28745 were converted to OLE studies to provide participants, including those in the placebo group, the opportunity for treatment with higher doses of gantenerumab expected to have a clinically meaningful effect. Doses up to 1200 mg SC Q4W of G3 gantenerumab are being tested, using dosing regimens designed to minimize the risk of ARIAs and taking into account the *APOE* genotype and the previous double-blind treatment and dose.

As of *23 October* 2017, *383* patients had been enrolled in the OLE studies WN25203 and WN28745, with *349* patients exposed to G3 gantenerumab doses higher than 225 mg (i.e., more than the highest repeat dose previously tested in AD patients) and *260* patients having reached the OLE target 1200-mg dose. ISRs and ARIAs remain the identified risks for gantenerumab. Safety data and MRI findings *have been* monitored by *an* iDMC, which has not identified any new safety signal in these ongoing studies.

1.2.2.5 *Study WP40052*

A total of 114 healthy male and female subjects received a single dose of 600 mg of gantenerumab high concentration, liquid formulation (containing gantenerumab manufactured by either G3 or G4 process, N=57 in each treatment group). The results showed that the plasma exposure in terms of area under the concentration–time curve from Time 0 to infinity (AUC_{inf}) was approximately 1.18 fold higher after SC administration of material manufactured by G4 process compared with material manufactured by G3 process, whereas C_{max} was similar (1.05 fold higher after administration of G4 material). Single-dose SC administration of 600 mg of gantenerumab as G3 or G4 material was safe and well tolerated.

Refer to the Gantenerumab Investigator's Brochure for details on nonclinical and clinical studies.

1.2.3 Safety Overview

Nonclinical characterization of gantenerumab did not show *any* relevant safety findings. To date, ARIAs and injection-site reactions (ISRs) are the identified risks for gantenerumab. No differences between active and placebo groups have been observed in laboratory parameters, physical and neurological examinations, vital signs, or electrocardiogram (ECG) parameters.

Amyloid-Related Imaging Abnormalities

In the double-blind portion of Study WN25203 (prodromal AD), ARIA events were time, dose, and *APOE* ε4 allele status dependent. The incidence of ARIA-E was 0.8% in the placebo, 6.6% in the 105-mg gantenerumab, and 13.5% in the 225-mg gantenerumab groups. For ARIA-H, the incidence was 13.2% in the placebo, and 22.9% and 16.2% in the 105-mg and 225-mg gantenerumab treatment groups, respectively. The rates of new ARIA-E were highest between 3 and 6 months of treatment (3.8% and 7.5% in the 105-mg and 225-mg gantenerumab groups, respectively) and decreased substantially after the first year of treatment (incidence of up to 2.3% in the 225-mg gantenerumab group in approximately 2 years). The median MRI Barkhof grand total score (BGTS) (Barkhof et al. 2013) of these findings was 3. Five patients (1.8%) from the 105-mg gantenerumab arm and 6 patients (2.3%) from the 225-mg gantenerumab arm experienced symptoms related to ARIA findings. Overall, most ARIA events were asymptomatic, non-serious, and of mild severity, except one serious adverse event of "partial seizures." Otherwise, the most commonly reported symptom was "headaches."

Following the futility analysis for Study WN25203, recruitment of the Phase III study (WN28745) was stopped. From 389 randomized patients, 387 patients were dosed with double-blind treatment (safety population), 192 patients in the gantenerumab arm and 195 patients in the placebo arm. Treatment in the double-blind phase was discontinued in July 2017 (median double-blind treatment duration: 68 weeks) and consenting patients transitioned into OLE. As of 16 January 2018, the double-blind part of Study WN28745 is ongoing with a small number of patients still in the post-treatment follow-up phase.

In the double-blind part of Study WN28745, the frequency of ARIA-E was 1.5% and 11.5% in the placebo and gantenerumab group, respectively. The frequency of ARIA-H was 11.8% and 15.6% in the placebo and gantenerumab group, respectively. The median BGTS of ARIA-E was 3. Overall, most ARIA events were asymptomatic, with only 2 patients (1.0%) in the gantenerumab group reported as having experienced a symptom related to ARIA (a non-serious and mild dizziness, and a non-serious and moderate headache).

The WN25203 and WN28745 OLE studies are ongoing and consequently, data are still *accruing*. As of *23 October* 2017, *383* patients had been enrolled and *377* dosed; *349* patients had their dose uptitrated to doses higher than 225 mg, and *260* patients were dosed with at least one gantenerumab dosage of *1200* mg.

Of the *377* patients dosed, *350* patients had undergone at least *one* postbaseline MRI scan. *In the WN25203 OLE study, 32 out of 133 patients with a postbaseline scan (24.1*%) had new ARIA-E *(*median maximum BGTS *was 6.5). In the* WN28745 *OLE study, 61 out of 217 patients with a postbaseline scan (28.1%) had new ARIA-E (median maximum BGTS was 8.0).* Most ARIA-E cases were asymptomatic; associated symptoms were reported for *20 of 93* patients *who had ARIA-E (2 patients* exposed to 225 mg of gantenerumab, *4* to 450 mg, 2 to 600 mg, *4* to 900 mg, and *8* to 1200 mg). The most frequently reported symptoms included visual impairment, dizziness, confusion, headache, and worsening of memory. Of the*20* symptomatic cases, there were *five* serious events*: one case of confusion resulting in hospitalization, one case of a possible ischemic stroke, and three cases of seizure/epilepsy. In two of the epilepsy cases, the seizure/epilepsy resolved in the absence of any specific* treatment within 24 hours*. In the third case, the patient was given antiepileptic treatment (phenobarbital and phenytoin; phenytoin was subsequently replaced by lacosamide due to an orticarioid reaction). The patient also had several electroencephalograms that showed a reduction in epileptic discharge*.

Twenty-three patients had ARIA-H events only (i.e., without concomitant ARIA-E); no symptoms were reported.

Injection-Site Reactions

In *the double-blind part of* Study WN25203, the overall incidence of ISRs was 15.4%, with the majority of the events being of mild intensity and resolved spontaneously. The incidence of ISRs was 4.5%, 18.8%, and 23.1% in the placebo, 105-mg gantenerumab, and 225-mg gantenerumab groups, respectively.

In the double-blind part of Study WN28745, the incidence of ISRs was 1.0% and 8.9% in the placebo and gantenerumab group, respectively. All ISRs were non-serious and mild in intensity; the vast majority resolved without treatment. The most common signs and symptoms included injection site erythema and injection site itching. No patients discontinued study treatment due to ISR.

As of *23 October* 2017, ISRs were reported in *93* patients (*24.7*%) across the OLE studies WN25203 and WN28745 and *9* patients received treatment for these events. The most common symptom was localized erythema. None of the events were serious or led to study drug discontinuation. One patient reported a severe event, injection-site pain after receiving a 600-mg dose by means of a pump, resulting in modification *of* uptitration. Most of ISRs were mild, resolved without treatment, and led to dose modification in only one case.

The Sponsor performs regular reviews of *OLE Studies WN25203 and WN28745* data and, to date has not identified any new or unexpected safety findings. In addition, an independent Data Monitoring Committee (iDMC) *reviewed* data at quarterly intervals and the conclusion of the last meeting (held on *15 December* 2017) was that the studies continue without modifications.

For safety data from all studies, refer to the Gantenerumab Investigator's Brochure.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Currently, approved therapies for AD focus on symptomatic approaches that target synaptic function and cognitive enhancement (Cummings 2004). However, the amyloid hypothesis suggests that overproduction of Aβ or failure to effectively clear this peptide contributes to AD (Selkoe and Hardy 2016) and that accumulation of Aβ peptides is one factor contributing to AD progression (Sun et al. 2015). Thus, the targeting of Aβ and subsequent displacement of Aβ from the brain is a rational approach to modify AD progression.

Despite compelling results in AD animal models (Wisniewski and Goñi 2014), clinical success with passive immunization targeting brain amyloid in global Phase III trials remains an unachieved goal. It has been suggested that lack of sufficient target engagement of anti-amyloid antibodies has been a factor in the failure of these Phase III studies (Cummings et al. 2016). An important advancement for therapies targeting aggregated amyloid was provided based on data from the Phase Ib PRIME study of aducanumab (Biogen) (Sevigny et al. 2016).

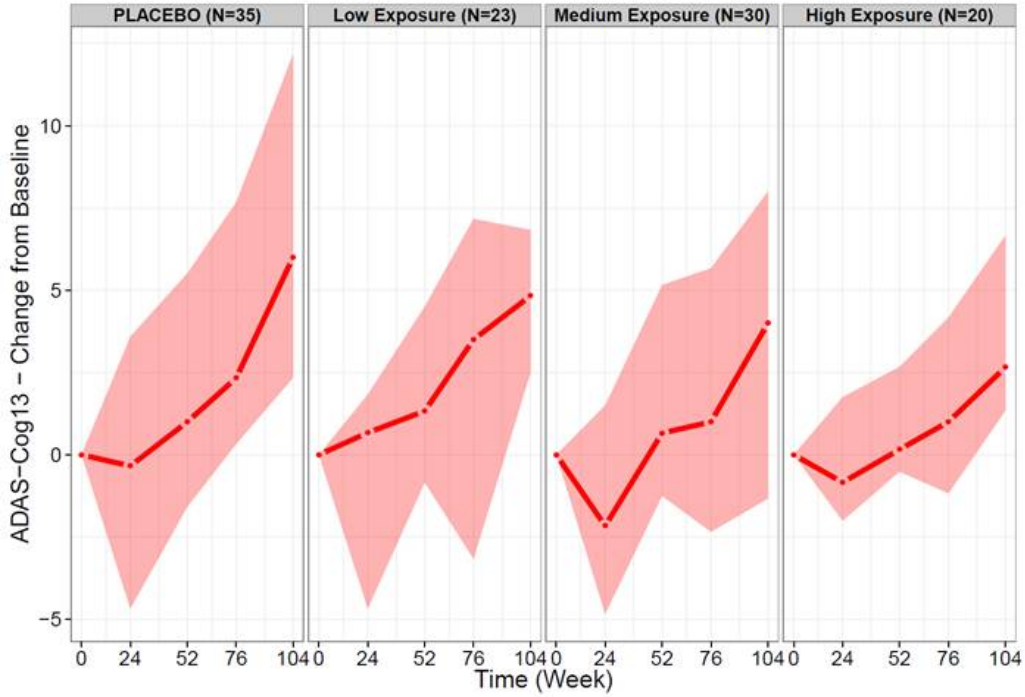
Aducanumab is a fully human IgG1 monoclonal antibody with similar PK and PD properties as gantenerumab that binds to aggregated target fibrillary and oligomeric forms of Aβ through microglia-mediated clearance of amyloid plaques (Sevigny et al. 2016). The results from the PRIME study showed that monthly IV injections of aducanumab for 1 year led to a dose- and time-dependent reduction of amyloid plaques in the brain. In addition, in patients with *early* (prodromal to mild) AD, a slowing of clinical decline, as measured on the Clinical Dementia Rating–Sum of Boxes (CDR-SOB) and Mini-Mental State Examination (MMSE) scores, has also been observed providing support to the hypothesis that Aβ plaque reduction confers clinical benefit.

1.3.1 Study Rationale

The results of the preplanned futility analysis of data from approximately 300 patients in Study WN25203 revealed the low likelihood for trial success with the original doses studied. Indeed, no significant differences were observed on any cognitive or functional measures (i.e., CDR-SOB, MMSE, Alzheimer Disease Assessment Scale–Cognition, Subscale 13 [ADAS-Cog13], and Functional Activities Questionnaire [FAQ]) or in a subgroup analysis of baseline characteristics (demographics, cognitive, CSF biomarkers, disease severity, or *APOE* ε4 allele status). Additional post-hoc analyses indicated that the overall rate of clinical decline was lower than expected for this study population (and with higher-than-expected proportion of "slow progressors") and strongly suggested that the doses studied in Study WN25203 (105 and 225 mg) were subtherapeutic and that a higher gantenerumab dose may have a clinically relevant effect *(Ostrowitzki et al. 2017)*.

Results of the post-hoc analyses of patients who were predicted to be progressors using a model derived from the Alzheimer's Disease Neuroimaging Initiative data (Delor et al. 2013) showed a drug concentration-dependent effect on clinical decline present for the ADAS-Cog13, MMSE, and Cambridge Neuropsychological Test Automated Battery results. Figure 1 displays the effects on increasing plasma gantenerumab concentrations (three concentration groups) on ADAS-Cog13 decline over the 2-year study. Greater concentrations of gantenerumab were associated with less clinical decline.

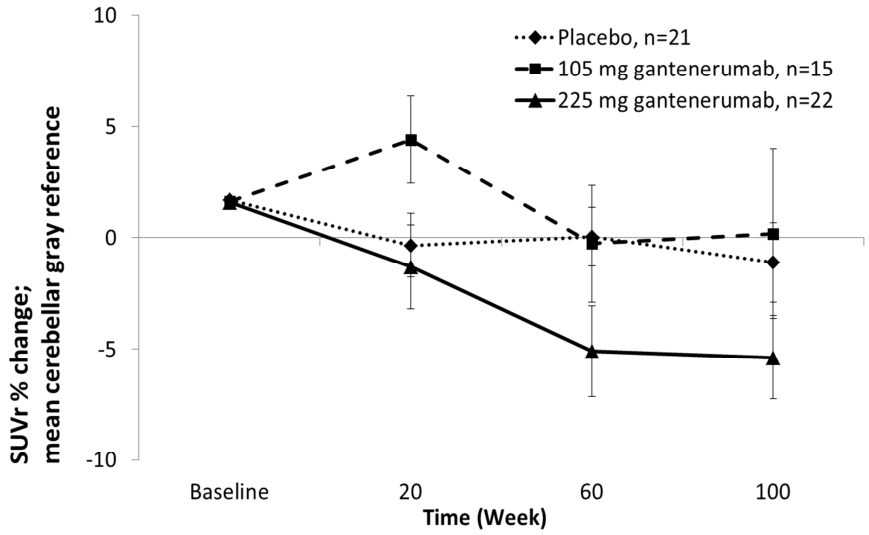
Figure 1 ADAS-Cog13 Treatment Response by Plasma Concentration: Two-Year Completing Fast Progressors in Study WN25203



ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13.
Notes: low exposure = 1.48–5 μg/mL; medium exposure = 5–10 μg/mL; high exposure = 10–26.68 μg/mL. Line = median; shaded = 50% observations.

Furthermore, a PET substudy of Study WN25203 using florbetapir F 18 confirmed a reduction in brain amyloid in gantenerumab-treated patients in a larger, less-impaired patient sample compared with Study NN19866, which had also demonstrated reduced accumulation of brain amyloid. Time-dependent reductions in SUVr were observed in patients treated with 225 mg of gantenerumab compared with placebo using the composite cortical SUVr and reference region of mean cerebellar gray. Week 100 results showed the mean percent change from baseline in SUVr was −1.09%, 0.72%, and −4.82% in the placebo, 105-mg gantenerumab, and 225-mg gantenerumab groups, respectively (see Figure 2). A small number of patients (n = 8) continued to receive 225 mg of gantenerumab for approximately 3 years (Week 156). Analysis suggested that the effect on SUVr reduction was continuous over time because SUVr reductions observed with the 225-mg dose of gantenerumab relative to placebo increased with the duration of long-term exposure, suggesting a sustained effect with continued exposure.

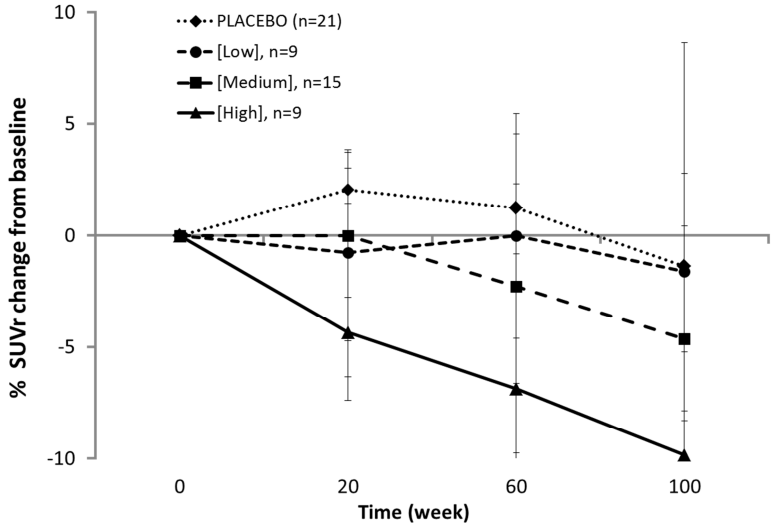
Figure 2 Mean Percent Change from Baseline in Composite Amyloid PET SUVr by Cerebellum Gray Reference: Study WN25203, PET Substudy



PET = positron emission tomography; SUVr = standardized uptake value ratio.

In Study WN25203, a concentration-based analysis of the PET results showed a clear response relationship between gantenerumab concentration in plasma and SUVr reduction, with greater mean concentrations resulting in greater amyloid clearance. As depicted in Figure 3, small changes in SUVr were present in the placebo and 1.9–5-μg/mL gantenerumab groups, whereas the higher concentration groups (5–10 μg/mL gantenerumab and 10–20.72 μg/mL gantenerumab) displayed SUVr reductions of up to 5% and 10%, respectively. These analyses indicate that higher doses may produce greater Aβ clearance that may translate into greater clinical effect.

Figure 3 Median Changes over Time in Concentration-Dependent PET SUVr by Gantenerumab Serum Concentration and Cerebellum Gray Reference: Study WN25203, PET Substudy



PET = positron emission tomography; SUVr = standardized uptake value ratio.
Note: low = 1.9–5 μg/mL; medium = 5–10 μg/mL; high = 10–20.7 μg/mL.

In addition, CSF analyses performed in Study WN25203 showed dose-dependent reductions in both CSF tau species (total tau [t-tau] and phosphorylated tau [p-tau]) in patients receiving gantenerumab compared with placebo. No change in CSF $A\beta_{42}$ was present over the 2-year period, as expected, given the mechanism of action of gantenerumab that targets fibrillar over monomeric Aβ.

Overall, these findings indicate the presence of clinical and biological effects of gantenerumab in subjects who had the highest exposure. In overall study population, results from the futility analysis of Study WN25203 indicated that the likelihood of the 225-mg dose of gantenerumab achieving a clinical effect was very low. These findings indicate that higher doses are required to achieve a clinical effect associated with the biological activity indicated by the amyloid and tau biomarker findings in Study WN25203. As a result, the decision was made to convert Studies WN25203 and WN28745 into OLE studies to give all patients the opportunity to receive higher doses of gantenerumab and to assess the safety of higher doses.

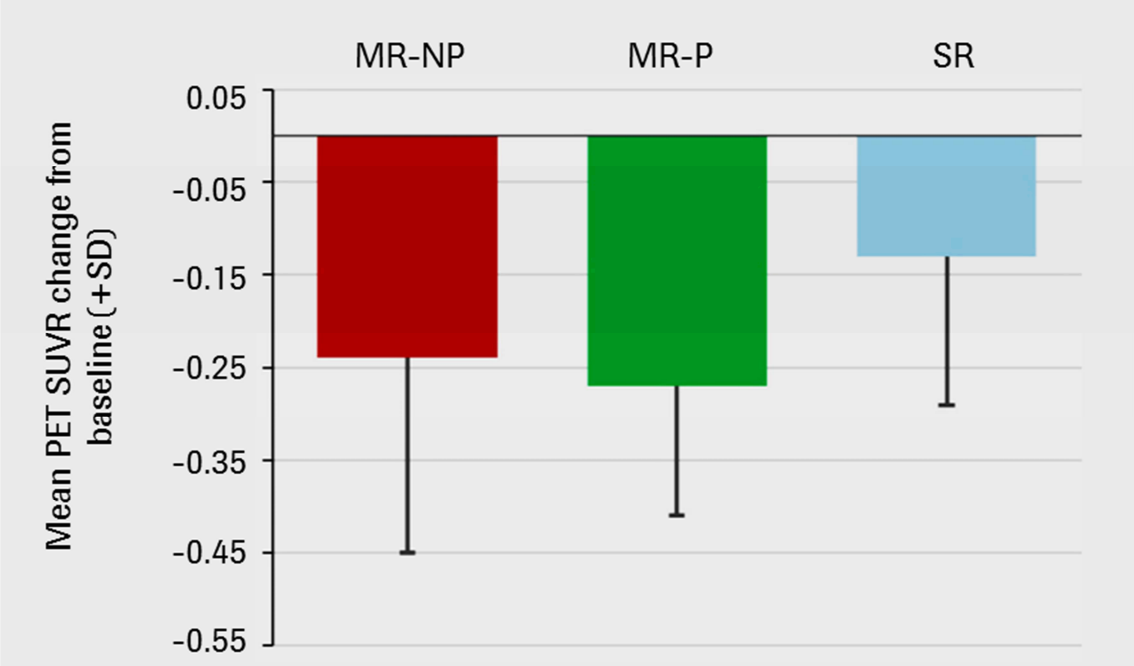
Additional support for using higher doses of gantenerumab comes from PK-PD models. Based on the established similarities between gantenerumab and aducanumab *(see* Section 1.3*)*, a model characterizing the relationship between *plasma* drug concentration (PK) and PET response (i.e., the PD effect on amyloid load in the brain) was derived from both gantenerumab study WN25203 data and aducanumab PRIME data to determine the target dose of gantenerumab for the OLE studies (for further details see

Appendix 4). In the OLE studies, the 1200-mg dose of SC gantenerumab Q4W is predicted to achieve plasma levels comparable to 10 mg/kg of IV aducanumab Q4W and to be associated with a comparable (~20%) amyloid brain reduction, which, in the case of aducanumab, was associated with a statistically significant clinical effect after 1 year of treatment. In order to minimize the occurrence of ARIA-E while achieving the target dose within a reasonable time frame, several titration schedules have been explored in the WN25205 OLE and WN8745 OLE studies.

Gantenerumab PK-PET models of amyloid reduction have been confirmed by PET data from the OLE studies. There were 85 patients from the OLE studies included in an amyloid PET substudy using florbetapir F 18 (Amyvid™). As of 31 August 2017, 40 patients treated with a dose of 900-mg to 1200-mg gantenerumab for ⩾6 months had a PET scan at Week 52 of the OLE studies. Patients were divided into three groups for analyses purposes, based on the study and on the double-blind treatment prior to switching to open-label gantenerumab and dose increase: Study WN28745 placebo (Marguerite RoAD non-pretreated [MR-NP], in the placebo arm during the double-blind part, N=14), Study WN28745 pretreated (Marguerite RoAD pretreated [MR-P], active arm during the double-blind part, low-dose gantenerumab, ⩽ 225 mg, N=17), and Study WN25203 (SCarlet RoAD [SR], off-treatment for approximately 78 weeks median, N=9). Across the three groups, there was a 7%–16% reduction in PET composite SUVr from baseline using the pre-specified cerebellar grey reference region, which was a 2- to 3-fold increase in the reduction observed in the double-blind WN25203-PET substudy with 225-mg gantenerumab after 2 years of treatment and in a good alignment with the PK-PET efficacy model (Figure 4). Also, approximately one-third of patients in the OLE PET substudy fell below the quantitative amyloid positivity threshold after 1-year titration and with 6–9 months at higher doses (⩾ 900 mg). PET scans with a quantitative amyloid level below threshold were shown to be concordant with a negative visual amyloid PET read and consistent with sparse to no neuritic amyloid plaques in histopathology verified studies (Joshi et al. 2012). Based on this data, it is expected that after 2 years of treatment on higher-dose gantenerumab, most patients may have an amyloid burden within the range typical of a healthy age-matched population. Taken together, these results strongly confirm the gantenerumab mechanism of action and support selection of target dose for Study WN29922 (see Section 1.2.3).

Figure 4 shows the reduction of brain amyloid PET SUVr in patients exposed to at least 900 mg for 6–9 months in the WN25203 (SCarlet RoAD) and WN28745 (Marguerite RoAD) OLE studies. Analysis is stratified by patients from the Marguerite RoAD non-pretreated (MR-NP) arm in the double-blind study, Marguerite RoAD pretreated (MR-P) arm, and the SCarlet RoAD study (SR).

Figure 4 Reduction of Brain Amyloid PET SUVr in Patients Exposed to at Least 900 mg for 6–9 Months in WN25203 (SCarlet RoAD) and WN28745 (Marguerite RoAD) Open-Label Extension Studies



MR-NP = Marguerite RoAD (WN28745) non-pretreated, N=14; MR-P = Marguerite RoAD (WN28745) pretreated, N=17; PET = positron emission tomography; SD = standard deviation; SR = Scarlet RoAD (WN25203, N=9); SUVr = standardized uptake value ratio.

1.3.2 *Rationale for Dosing Strategy*

As indicated in Section 1.3.1, the target dose of 1200 mg G3 material administered in the WN25203 and WN28745 OLE studies has been identified based on PK-PD modeling and simulations (details about the model are presented in Appendix 4) and is predicted to lead to an amyloid PET reduction similar to 10 mg/kg IV aducanumab Q4W. The OLE PET data have shown been consistent with these predictions.

In the OLE studies WN25203 and WN28745, patients were allocated to different titration schedules (two schedules in Study WN25203 and four schedules in Study WN28745) according to their *APOE* allele status and treatment arm during the double-blind period of the parent studies. These titration schedules were implemented in order to mitigate the risk of ARIA events. A*n ARIA-E hazard model* was first developed *on* bapineuzemab *data* (Hutmacher et al. 2013). This model, which includes drug concentrations, time since first dose, and *APOE* ε4 allele status, was applied to the double-blind results in Study WN25203; the model was then tested on publicly available aducanumab data from the PRIME study and were used to predict the incidence of ARIA-E events with a high degree of accuracy, including the observed ARIA-E rate differences across *APOE* ε4 allele groups.

Recently, the ARIA-E hazard model has been updated with observations from the WN25203 and WN28745 OLE trials using higher doses of gantenerumab (see Appendix 5).

*Using the validated PK-PET and ARIA-E hazard model, m*ultiple titration options have been simulated, including separate simulations for *APOE* ε4 allele carriers and non-carriers. Two different types of titration schedules, reflecting the different risk for ARIA events between *APOE* ε4 allele carriers and non-carriers were considered. Although an *APOE* ε4 genotype–based titration regimen could permit *APOE* ε4 non-carriers to achieve the target dose more quickly, an option with a single, slower titration schedule for all patients is favored as it provides an overall lower risk for ARIA. Given the chronic and gradually progressive nature of AD, the favored option is a single, slow titration schedule for all patients because it is simpler for clinicians, less prone to error, and does not require *APOE* genotyping before the initiation of treatment.

Thus, based on the information from the WN25203 and WN28745 OLE studies, in which gantenerumab (manufactured with G3 process) up to 1200 mg Q4W was assessed and shown to be safe for APOE ε4 allele carriers and non-carriers, and based on the internally developed PK-PD models, the following dosing regimen for Study WN29922 was selected: 150 mg Q4W for 3 months, then 300 mg Q4W for 3 months, and then 600 mg Q4W for 3 months, followed by 600 mg Q2W until the end of the study. The switch to a Q2W administration schedule allows patients to decrease the number of SC administrations in the abdomen per visit.

The PK-PD models referenced above were developed based on information from the G3 material and were used to establish the initial dosing regimen for this study. As indicated previously, gantenerumab drug substance manufacturing process was optimized from G3 to G4, and a relative bioavailability study (WP40052) assessed the pharmacokinetic difference between the G3 and G4 material in humans.

The results of this relative bioavailability study (WP40052) show that the AUC_{inf} is approximately 1.18 fold and the C_{max} is approximately 1.05 fold higher after administration of G4 compared with G3. As AUC is considered the driver of the treatment effect, the conversion factor of 1.18 from the G3 to G4 material has been based on the AUC_{inf}. The association between microglial-driven removal of aggregated brain amyloid and AUC has been shown in preclinical experiments and clinical studies. In addition, as gantenerumab exhibits linear pharmacokinetics, the AUC_{inf} after single dose reflects the steady state exposure (AUC_{tau}) after multiple doses.

Based on the above rationale and the fact that gantenerumab manufactured with G4 process was safe and well tolerated, the G3 dosing regimen has been converted into the following G4 dosing regimen for the WN29922 study: 120 mg Q4W for 3 months, then 255 mg Q4W for 3 months, and then 510 mg Q4W for 3months, followed by 510 mg Q2W until the end of the study. This schedule enables titration to target dose within

9 months (see Table 1), with predicted overall ARIA-E rate of approximately 26% based on the current ARIA-E hazard model. The low starting doses and gradual increase in dosing (i.e., slow titration schedule) are expected to reduce the risk of ARIA-E for both APOE carriers and non-carriers. An MRI scan, confirming the absence of ARIA-E findings, will be required prior to each dose increase.

Table 1 Proposed Dose and Titration Regimen for Phase III Studies

Month	1	2	3	4	5	6	7	8	9	10
Dosing frequency	*Q4W*	*Q4W*	*Q4W*	*Q4W*	*Q4W*	*Q4W*	*Q4W*	*Q4W*	*Q4W*	*Q2W*
Dose (mg)	*120*	*120*	*120*	*255*	*255*	*255*	*510*	*510*	*510*	*510*

1.3.3 Risk-Mitigation Measures for ARIA Findings

ARIA is the most significant adverse event reported in therapies against aggregated forms of Aβ. These findings appear to be dose, time, and *APOE* ε4 allele dependent (Piazza and Winblad 2016).

The mechanism underlying the development of ARIA-E and ARIA-H during anti-amyloid treatment is unknown. Because antibodies target removal of Aβ from both the parenchyma and cerebral vasculature, vessels with preexisting amyloid vascular pathology might become transiently more susceptible to leakage of vascular contents. This pathology results in ARIA-E if the leakage consists of proteinaceous fluid and in ARIA-H if the leakage consists of blood products (Sperling et al. 2012).

*Thus, a*n anti-Aβ therapy that effectively maintains vascular β-amyloid clearance would allow *vascular remodeling and may,* with time, *decrease* the risk of such extravasation events *(Sperling et al. 2012)*. This is consistent with experience in previous and ongoing studies and with reported data from the long-term extension study of aducanumab treatment (Viglietta et al. 2016).

Previous and ongoing studies with gantenerumab showed that ARIAs are manageable with MRI monitoring and dose intervention algorithms (i.e., temporary study drug interruption or temporary suspension of uptitration) and that these events are mostly asymptomatic. Recent data from the long-term extension of the PRIME study (aducanumab) suggested also that a titration up to 10 mg/kg (predicted to be comparable to 1200 mg of SC *Q4W* G3 gantenerumab (or *510* mg of *SC Q2W* G4 gantenerumab) per the *PK-PD* model (see Appendix 4) may reduce the incidence of ARIA-E compared with higher fixed dosing (Viglietta et al. 2016).

In Study WN29922, imaging-related criteria will be used to exclude patients with clinically important cerebral vascular disease at baseline, as well as ARIA-related lesions. A slow titration schedule will be implemented to reach the target dose, and MRI monitoring will be conducted during the study at regular intervals (see Appendix 1, *and*

Tables 1 and 2, for the schedule of activities for the uptitration and MRI schedules). An MRI scan documenting the absence of ARIA-E findings will be required prior to each dose increase. If ARIA findings occur, more intense MRI monitoring, dose adjustments, temporary dose holding, or permanent discontinuation will be implemented according to an ARIA-related dose-adjustment plan, described in Section *5.1.3*. Safety findings (including unblinded individual patient and aggregate data) will be reviewed on a regular basis by the iDMC.

1.3.4 Risk to Patients without Alzheimer's Disease Pathology

Owing to the rigorous screening procedures in this study, including measurement of the CSF tau to $A\beta_{42}$ ratio and/or amyloid PET scan, it is *anticipated* that only patients with AD pathology will be enrolled. In the event that a patient without amyloid pathology is enrolled, no additional risk is expected. However, such patients may still experience side effects related to administration of gantenerumab (e.g., ISRs and development of anti-drug antibodies [ADAs]).

1.3.5 Overall Benefit–Risk Summary

Overall, the benefit–risk assessment of gantenerumab is based on the following:

- Gantenerumab *has* shown evidence of reducing amyloid plaques (i.e., observed evidence of brain amyloid reduction*)* and, thus, shows potential benefit in slowing the progression of AD.
- Findings from the WN25203 and aducanumab PRIME studies provide additional support for the hypothesis that anti-amyloid treatment may be associated with a beneficial clinical effect.
- Results from the double-blind portion of Study WN25203, as well as from the OLE studies WN25203 and WN28745, showed that ARIA findings are mostly asymptomatic, non-serious, of mild severity*,* and do not require permanent cessation of treatment*. ARIAs are manageable with MRI monitoring and dose intervention algorithms, as detailed in Section 5.1.3*.
- *No new safety signal has been identified in the d*ata from the ongoing OLE studies *with* doses of up to 1200 mg *Q4W G3 material. These data support the administration of the target dose of 510 mg Q2W G4 material to both ApoE ε4 carriers and non-carriers in the WN29922 study.*

Thus, the anticipated benefit–risk profile of gantenerumab supports clinical trials with higher doses in the population with *early (*prodromal to mild*)* AD.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of gantenerumab compared with placebo in patients with *early (*prodromal to mild*)* AD. Specific objectives and corresponding endpoints for the study are outlined in Table 2.

Table 2 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of gantenerumab administered by SC injection compared with placebo	• The change from baseline (Day 1) to Week 104 in global outcome, as measured by the CDR-SOB
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo on cognition and function	The change from baseline to Week 104 in cognition and/or function, as measured by: • MMSE total score • ADAS-*Cog11 and* ADAS-Cog13 • Verbal Fluency Task • *Coding* • FAQ • ADCS-ADL total score *and instrumental score*
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo	The change from baseline to Week 104 in the following: • Time to clinically evident decline, defined as an increase of ≥2.0 in CDR-SOB subscore or ≥1 in at least four items of the FAQ • *Severity*, as assessed by the CDR Global Score • Function, as assessed by the CDR function subscore • Dependence level, as derived from the ADCS-ADL score • Cognition, as measured by the CDR cognition subscore • Health-related quality of life, as assessed by the QoL-AD scale • Behavioral and *neuropsychiatric* symptoms of AD, as measured by the NPI-Q • Study partner burden, as assessed by the ZCI-AD scale • Elements of resource utilization, as assessed by the RUD-Lite • Health outcomes in patient and study partner, as measured by EQ-5D questionnaire

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

Table 2 Objectives and Corresponding Endpoints (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of gantenerumab compared with placebo	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Presence of ADAs during the study relative to the presence of ADAs at baseline
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the PK profile of gantenerumab	• Plasma concentration of gantenerumab (administered subcutaneously) at specified timepoints
Pharmacodynamic Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo in patients with *early (*prodromal to mild*)* Alzheimer's disease	• Change from baseline in brain amyloid load, as measured by amyloid PET scan in a subset of patients • Change from baseline in brain tau load, as measured by tau PET scan in a subset of patients • Change from baseline in cerebral spinal fluid markers of disease in a subset of patients, including, but not limited to, $A\beta_{1-42}$, total tau, and phosphorylated tau • MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all patients
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo in patients with *early (*prodromal to mild*)* Alzheimer's disease	Plasma pharmacodynamic biomarkers Change from baseline to Week 104 in functional brain connectivity, as measured by resting-state functional MRI (where available) Change from baseline to Week 104 in *integrity of white matter*, as measured by DTI-MRI (where available)

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of gantenerumab in patients with *early* (prodromal to mild) AD.

The planned number of patients for the global enrollment phase for the study is approximately *760* patients: randomized in a 1:1 ratio to receive gantenerumab and placebo (*380* patients randomized to gantenerumab and *380* randomized to placebo). To maintain a balanced number of patients enrolled in each treatment arm and to ensure that the arms are comparable, randomization will be stratified by stage of disease (prodromal AD vs. mild AD), APOE allele status (presence vs. absence of the ε4 allele), use of AD medication (presence vs. absent), geographic region (*Western Europe vs. Rest of the World vs. North America*) and participation in longitudinal amyloid *and tau* PET *substudies*. Approximately *175* centers in approximately *15* countries worldwide will participate in this study.

Patients will be selected on the basis of clinical diagnosis of probable AD (according to the National Institute on Aging/Alzheimer's Association [NIA/AA] diagnostic criteria and guidelines for AD; see Appendix 2) (McKhann et al. 2011) or prodromal AD (according to the NIA/AA diagnostic criteria and guidelines for mild cognitive impairment (MCI) due to AD; see Appendix 3) (Albert et al. 2011). *The aim of the study is to recruit approximately 50% of the participants with prodromal AD.*

Eligible patients will be 50–90 years old, inclusive, must show evidence of β-amyloid pathology as indicated by the CSF tau to Aβ42 ratio (CSF-enrolled patients) or positive amyloid PET scan by visual read (PET-enrolled patients), and meet eligibility criteria as detailed in Section 4.1.

The study will consist of a screening period of up to *12* weeks in length following the signing of informed consent. *Sites also have* the option to prescreen patients on the Free and Cued Selective Reminding Test (FCSRT) *and MMSE*. Patients must sign a separate Informed Consent Form before administration of *these tests* if used for prescreening. If the results confirm a patient's eligibility, then the FCSRT *and MMSE* will not have to be completed again during the screening period as long as the test has been done within 12 weeks prior the baseline.

Eligible patients will then undergo baseline visit assessments (Day 1) prior to receiving the first dose of blinded study drug (gantenerumab or placebo). Patients will continue in the double-blind treatment period for 104 weeks. Visits and study drug administration will occur Q4W until patients reach the *target dose*, which will be *510* mg Q2W. After the last dose of study drug (Week 102), final efficacy and safety assessments will be

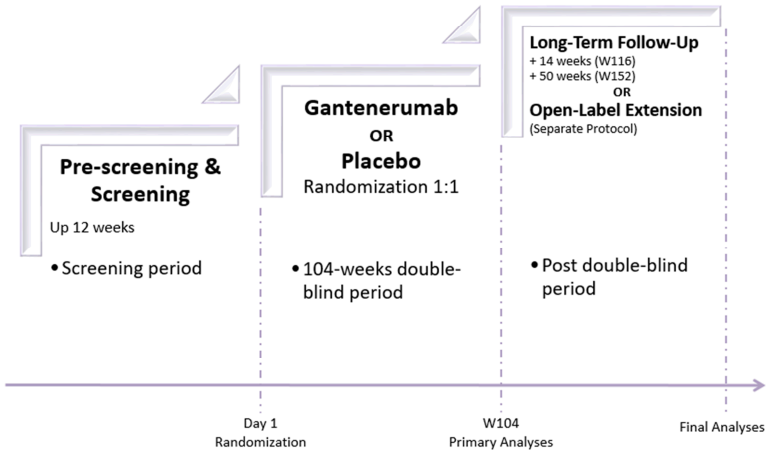
performed 2 weeks later (Week 104). Patients may then enroll in *an* OLE study *if eligible*. Patients who do not enter the OLE study will have additional follow-up visits at 14 and 50 weeks after the last dose for safety and limited efficacy assessments (Weeks 116 and 152, respectively). *Patients who prematurely discontinue treatment will continue in the double-blind treatment period and will be asked to return for collection of safety and limited efficacy data (see Section 4.7.1).*

Patients will undergo brain MRI examinations for safety monitoring and longitudinal changes in brain structure. MRI scans will be read by a central MRI reader (for more details regarding imaging-related criteria, see Section 4.1.2.2). Patients will also undergo standard tests to monitor safety (blood tests, ECG), as well as the Columbia–Suicide Severity Rating Scale (C-SSRS) to monitor for suicidality, tests for cognition, function, and quality-of-life (QoL) status. Blood samples for the assessment of PK samples, PD biomarkers, and anti-drug antibodies will be obtained from all patients.

The incidence and nature of adverse events, serious adverse events, ARIA-E and ARIA-H, adverse events of special interest, ECGs, and laboratory abnormalities will be assessed on a regular basis by an unblinded iDMC.

An overview of the study design is provided in Figure 5. The schedule of activities provided in Appendix 1.

Figure 5 Overall Study Design



W = week.

The study consists of three distinct periods:

- Screening *(including an optional prescreening)*: The screening period may last up to *12* weeks for each eligible patient.
- Double-blind treatment period: After screening, patients who meet all eligibility criteria will be randomly assigned to one of two arms (gantenerumab or placebo) in a 1:1 ratio. Following baseline assessments, each patient will receive a minimum of nine SC Q4W administrations of study drug (uptitration period), followed by up to 34 SC Q2W administrations of study drug in the 104-week, double-blind treatment period. The last dose of study drug will be administered at Week 102. At the end of the double-blind treatment period, all participants will undergo a Week 104 visit in order to collect data for the primary analyses.
- Post–double-blind treatment period: After the Week 104 visit, patients will be asked to come back for the long-term follow-up visits or to continue in the OLE.

  Long-term follow-up: Long-term follow-up will consist of a 50-week follow-up period with evaluations at Weeks 14 and 50 after completion of study drug administration or early termination for patients who do not enter the OLE.

  OLE study: All eligible patients will have the opportunity to enter an OLE study (details will be provided in a separate protocol).

For the schedule of activities at each visit, see Appendix 1, Tables 1 and 2.

China Enrollment Plan

Based on historical data, patient recruitment are expected to take longer in China; therefore, a specific China enrollment plan has been established. Thus, if at least 1 patient is enrolled *at sites* in *mainland* China*, Hong Kong, and Taiwan that are recognized by the China Food and Drug Administration (CFDA)* during the global enrollment phase, additional patients may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. All patients enrolled *at CFDA-recognized sites* in the global enrollment *phase* will be included in the primary analysis.

3.1.2 Substudies

The substudies associated with Study WN29922 will be described in separate protocols, and patients consenting to enroll in these substudies will be asked to sign the associated Informed Consent Forms.

3.1.3 Data Monitoring Committee

The iDMC will evaluate patient safety and efficacy on a regular basis. In addition to the data defined in the iDMC Charter (e.g., the incidence and nature of adverse events, serious adverse events, and adverse events of special interest, ARIA-E and ARIA-H), the iDMC will review all necessary cumulative data at regular intervals during the study, including efficacy when needed. It is anticipated that these assessments will occur approximately every 3 months. At the time of each review, the iDMC will make

appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, the treatment regimen should be modified, the protocol should be amended, enrollment should be held pending further safety evaluations). The iDMC will also evaluate planned *or unplanned* interim analyses for efficacy or futility (see Section 6.7.1).

Decisions will be made in consideration of the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities will be detailed in the iDMC Charter.

Final decisions will rest with the Sponsor.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for safety analyses or safety follow-up is received for the last patient, whichever occurs later.

The study will consist of a screening period of up to 12 weeks *(*including the optional prescreening period) for each eligible patient who signs the Informed Consent Form and agrees to participate, followed by a double-blind treatment period of 102 weeks of study drug treatment plus a visit 2 weeks after the last dose (Week 104), and followed by the post–double-blind treatment period of two follow-up visits at 14 and 50 weeks after the last dose (Weeks 116 and 152, respectively). Thus, for a patient not entering the OLE, the maximum length of study is approximately *164 weeks*.

3.3 RATIONALE FOR STUDY DESIGN

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of gantenerumab in patients with *early (*prodromal to mild*)* AD, increased amyloid burden (defined according to CSF or PET criteria), and clinical symptoms.

3.3.1 Rationale for Patient Population

As the accumulation of Aβ brain amyloid begins before the onset of AD dementia, it is reasonable to postulate that the benefit of anti-amyloid therapy may be greater if initiated at an early stage of the disease. For this reason, Roche has focused clinical development of gantenerumab on *early (*prodromal to mild*)* AD.

Patients in this study are required to meet standard research criteria for mild AD (according to the NIA/AA research criteria and guidelines for AD; see Appendix 2) or prodromal AD (according to the NIA/AA research criteria and guidelines for MCI due to AD; see Appendix 3). Note that the terms “prodromal AD” and “MCI due to AD” are considered to refer to the same population in this study and are defined according to

NIA/AA research criteria and guidelines for MCI due to AD. Thus, patients with prodromal AD will present with documented objective evidence of deficit in one cognitive domain. Patients with mild AD must present with documented deficits in at least two cognitive domains and evidence of functional decline. Overall, the population will have an MMSE between 22 and 30 (inclusive) points and a CDR global score (CDR-GS) of 0.5 or 1.0. The MMSE score provides evidence of no more than mild disease severity and the CDR-GS score indicates that the patients have prodromal AD or cognitive and functional deficits consistent with mild AD. *The aim of the study is to recruit approximately 50% of the participants with prodromal AD.*

Gantenerumab is an antibody that targets Aβ. Thus, the study population should have documented evidence of amyloid pathology. This patient selection approach is consistent with the NIA/AA research diagnostic criteria and guidelines for AD as well as with the Qualification Opinion from the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use on the use of CSF biomarkers for enrichment of trials in mild to moderate AD dementia (2012), and the U.S. Food and Drug Administration (FDA's) draft guidance for early AD (2013). Although the FDA's guidance refers to the early stage of AD in which individuals present with clinical MCI, biomarkers of amyloid pathology are expected to add value to patient selection in mild AD studies, especially for anti-amyloid treatments (McKhann et al. 2011; Dubois et al. 2014, 2016). Biomarker enrichment is important for anti-amyloid therapy clinical trials because some results of early trials have demonstrated that approximately 20% patients who are enrolled in trials based on a clinical diagnosis of AD alone may not have underlying amyloid pathology as assessed by amyloid PET (Doody et al. 2014; Salloway et al. 2014).

For enrollment in this study, biomarker evidence of β-amyloid deposition will be assessed either by a centralized visual assessment of PET amyloid imaging, using one of the three *following* amyloid PET imaging tracers (Vizamyl™, Neuraceq™, and Amyvid™ according to country and site availability) or by the CSF tau to $A\beta_{42}$ ratio (using a prespecified cutoff and the Roche Diagnostics Elecsys immunoassay).

Both methods (CSF and PET) are established approaches to identify Aβ accumulation in the brain in vivo (Pannee et al. 2016; Vos et al. 2016) and both have been used in research and in clinical practice. There is also emerging evidence that indicates consistency between PET amyloid imaging and CSF biomarkers. Indeed, in biomarker research studies, concordance between amyloid PET and the combination of CSF $A\beta_{1-42}$ with t-tau has been shown to be very high with properly controlled CSF methodologies (EMA 2012).

To enrich for *patients who are* more likely to decline over the 2-year trial, all patients have to demonstrate amnestic deficits as measured by the FCSRT's total free recall score and cueing index (Sarazin et al. 2007). The use of the FCSRT to support a hippocampal-related memory deficit (Buschke 1984; Grober and Buschke 1987) has

been recommended by the International Working Group (IWG-1; Dubois et al. 2007, 2010). Indeed, the core clinical symptom of AD is significant and progressive episodic memory impairment. Memory impairments because of AD are known to be hippocampal dependent and are thought to be characterized by a deficit in recall, which is often not recovered with cueing.

The FCSRT is a cued recall test that uses controlled encoding to ensure that impaired recall and cueing results are due to memory impairment and are not a failure at encoding (e.g., by means of attentional impairment). The FCSRT has demonstrated high sensitivity and specificity in differentiating patients with AD from both healthy controls and patients with other forms of dementia (Grober et al. 2008, 2010). More recently, the choice of the FCSRT as a valid clinical marker for typical prodromal AD (amnestic MCI) has been endorsed by the IWG-2 (Dubois et al. 2014) and is supported by studies showing that this test is a good tool to use for predicting progression to AD for patients with prodromal AD (Mura et al. 2014; Lemos et al. 2015). In addition, data generated from Roche datasets showed that a cueing index of $\leq$0.67 is a good predictor of cognitive decline. Therefore, the FCSRT cueing index of $\leq$0.67 and a free recall score of $\leq$27 have been selected as inclusion criteria for this study. The cueing index measures the ability of a patient to benefit from being reminded using specific cue words to recall the target word. To prevent patients who have a high free recall and who do not appear to benefit from being reminded from being included simply because of apparent low cueing index, a free recall score of $\leq$27 will also be required. The FCSRT index is consistent with that published by Sarazin et al. (2007) and Auriacombe et al. (2010).

3.3.2 Rationale for Use of a Placebo Control Group

Study WN29922 is a placebo-controlled trial in which patients will be eligible for study participation whether or not patients are receiving standard-of-care medications for AD (i.e., *acetylcholinesterase inhibitors,* memantine, and/or medical *food supplements*). Given that there are currently no approved disease-modifying compounds that could serve as an active control, patients will be randomized to receive gantenerumab or placebo on top of background therapies.

3.3.3 Rationale for Gantenerumab Dosage and Titration Schedule

In the OLE studies, different titration schedules (based on prior double-blind treatment exposure and *APOE* ε4 status) have been utilized to enable all patients to reach a target dose of 1200 mg SC Q4W *while managing the risk for ARIA with MRI monitoring and dose intervention algorithms. In addition, d*ata from the OLE studies support treatment at a low starting dose with a gradual increase in dosing (i.e., slow titration schedule) to reach target dose and to reduce the risk of ARIA findings.

As presented in Section 1.3.2, *a target dose of 510 mg Q2W along with a titration schedule with a low starting dose and gradual increase in dosing (i.e., slow titration schedule) that is expected to reduce the risk of ARIA-E for both APOE carriers and non-carriers have been identified for the current study.*

Therefore, all patients in Study WN29922 (regardless of APOE ε4 status) will receive 120 mg of SC gantenerumab Q4W for 3 months, 255 mg SC Q4W for 3 months, and 510 mg SC Q4W for 3 months prior to reaching target dose of 510 mg Q2W after 9 months of titration (see Section 1.3.2 for additional details about the conversion of G3 dosing regimen to G4 dosing regimen). Based on the model predictions (see Appendix 5), the overall ARIA-E rate is expected to be approximately 26%. An MRI scan, confirming the absence of ARIA-E findings, will be required prior to each dose increase.

3.3.4 Rationale for Treatment Duration

According to the EMA's draft guidance on medicinal products for the treatment of AD and other dementias (EMA 2016), controlled clinical trials aimed at demonstrating short-term improvement in mild to moderate AD should last at least 6 months. In order to establish an effect on disease progression, a distinction between symptomatic and disease-modifying effects of a medicinal product has to be made. In addition to demonstrating a relationship between clinical outcomes and an effect on biomarkers of disease pathology, clinical improvement must be shown over a time period that is relevant to the proposed mechanism of action and the expected natural progression rate of the disease. In AD research, long-term placebo-controlled trials are needed in order to allow time for an efficacious therapy to reverse a longstanding disease process as well as to allow time for a sufficient number of placebo-treated patients to progress. Eighteen months was assumed to be of sufficient length in some recently completed Phase III studies of anti-Aβ antibodies (EMA 2016). In prodromal disease stages, even longer studies may be necessary. In addition, placebo decline is expected to be greater at 24 months relative to 18 months; this greater decline allows *an increased* potential to demonstrate a treatment effect.

A 2-year treatment duration has been selected as the most appropriate duration for assessment of the primary endpoint. The duration is based on the mechanism of action of gantenerumab, which is expected to delay and reduce AD progression over time compared with control. *As 9-month titration period to reach the target dose is needed, a 2-year treatment period may also be appropriate for the assessment of the primary endpoint.* To capture an earlier signal of efficacy, should it be present, assessments relevant to the study objectives will also be obtained at 6, 12, and 18 months.

3.3.5 Rationale for Long-Term Follow-Up

The primary objective of the long-term follow-up is to estimate the long-term safety of gantenerumab over an extended period of time. Study assessments performed 14 and 50 weeks after the last dose of study drug will be used to evaluate the effects of treatment on both efficacy and safety parameters over an extended period after study drug discontinuation. Assessments will be conducted for all patients who discontinue treatment during the study or who complete the study but do not enter the OLE study. Assessments will also allow for the exploration of the long-term effects with declining drug exposure.

3.3.5.1 Rationale for Duration of Study Follow-Up (14 Weeks)

The primary purpose of the 14-week follow-up visit (i.e., 14 weeks after the last dose) is to evaluate the long-term safety of gantenerumab. The apparent terminal half-life of gantenerumab is in the order of 24 days, and gantenerumab is cleared from plasma after approximately 16 weeks (approximately 5 half-lives). Therefore, safety assessments performed 14 weeks after the last dose are considered sufficient to evaluate residual effects on peripheral safety outcomes. In addition, efficacy assessments at the follow-up visit may support an enduring effect of gantenerumab after treatment is stopped.

3.3.5.2 Rationale for Long-Term Follow-Up (50 Weeks)

Assessments performed 50 weeks after the last dose will be used to evaluate the long-term effects of study drug on both efficacy and safety parameters. The assessments will allow for the exploration of the long-term effects of study drug given the expected level of decline over this period. Patients will not be restricted from starting new treatment and therefore, the analysis will be considered exploratory.

3.3.6 Rationale for Primary Outcome Measure: Clinical Dementia Rating–Sum of Boxes

AD is considered a continuous disease that passes through consecutive stages without discrete transition points. Thus, the use of a single endpoint across both subpopulations of *early* (prodromal to mild) AD is consistent with the current understanding of AD.

Showing the benefit of new therapies for patients in the early stages of AD is challenging, owing to the lack of sensitive assessment tools. Use of the CDR-SOB as the primary outcome measure for studies of *early* (prodromal to mild) AD enables simultaneous demonstration of benefit on primary symptoms and clinical relevance (Aisen 2009, 2011), while also ensuring use of a clinical outcome assessment with adequate measurement properties (FDA 2013).

The Washington University CDR is a global assessment instrument that yields global scores (GS) and SOB scores. The CDR is derived from a semi-structured interview with the patient and an appropriate informant, and it rates impairment in six categories (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) on a 5-point scale for which 0 = no impairment,

0.5=questionable impairment, and 1, 2, and 3=mild, moderate, and severe impairment, respectively. From the six individual category ratings, or box scores, the CDR-GS is established by clinical scoring rules, for which CDR 0=no dementia and CDR 0.5, 1, 2, or 3=questionable, mild, moderate, or severe dementia, respectively (Morris 1993). The CDR-SOB score is a detailed quantitative general index that provides more information than the CDR-GS in patients with *early* (prodromal to mild) dementia (Coley et al. 2011; Cedarbaum et al. 2013). In particular, the CDR-SOB has been proposed for use in longitudinal assessment of dementia and is widely used in AD studies as a global measure of disease progression (Williams et al. 2013). The FDA's draft guidance for developing drugs for the early stages of disease suggests that a composite scale, validated in patients with early-stage disease that includes both cognition and function as a single primary efficacy outcome measure, is appropriate. The CDR-SOB is an example of a measure that fulfills these criteria (FDA 2013) and is now being utilized as the sole primary endpoint in several studies utilizing patient populations with *early* (prodromal to mild) AD, including the CREAD (crenezumab) and PRIME (aducanumab) studies.

3.3.7 Rationale for Pharmacokinetic Sampling

A sparse sampling schedule is being utilized to minimize patient burden and yet provide an adequate characterization of the population PK profile of gantenerumab. The PK data may be combined with available data from other gantenerumab studies and may be used to assess exposure–response relationships for relevant imaging, CSF, plasma PD biomarkers, ECGs, and efficacy and safety outcomes in patients with *early* (prodromal to mild) AD, as appropriate.

3.3.8 Rationale for Biomarker Assessments

The following biomarker assessments described in Sections 3.3.8.1 (CSF), 3.3.8.2 (PET imaging), and 3.3.8.3 (brain volumetry, connectivity, and fiber tract integrity) will be used to investigate the effect of gantenerumab on the underlying pathology of AD in the patient population.

3.3.8.1 Cerebral Spinal Fluid Biomarkers

Amyloid plaque deposition, neurofibrillary tangle formation, and neuronal degeneration are known pathologic features of AD. Decreased CSF $A\beta_{1-42}$ and elevated CSF t-tau and p-tau are considered a biochemical signature of AD. Accumulating evidence suggests that low CSF $A\beta_{1-42}$ reflects underlying amyloid plaque pathology, whereas increased t-tau and p-tau levels may be reflective of neurodegeneration and/or tau pathology. Amyloid deposition may be the initiating event in the cascade of pathologic processes underlying AD, whereas tau pathology appears to be a subsequent event, and more associated with neurodegeneration. Therefore, t-tau and p-tau may be studied as downstream biomarkers of the primary target of anti-amyloid therapies such as gantenerumab.

Although biomarkers indicative of certain neuropathologies are not surrogate markers for efficacy, there is some evidence that anti-Aβ treatments may cause changes in these biomarkers. A neuropathologic study of patients with AD from Study AN1792 suggests that active amyloid immunotherapy ameliorates neurite abnormalities and tau pathology through decreased tau phosphorylation (Serrano-Pozo et al. 2010). In a pooled analysis of CSF data from two Phase II trials with bapineuzumab in patients with mild to moderate AD, a decrease in both p-tau and t-tau levels relative to baseline was observed in the bapineuzumab group after 12 months of therapy (Blennow et al. 2010). These findings were confirmed in two Phase III studies with bapineuzumab (Sperling et al. 2012) as well as in Study WN25203 with gantenerumab. In Study WN23203, CSF biomarkers were analyzed for changes in multiple proteins, including $A\beta_{1-42}$, t-tau, p-tau, and neurogranin, over the 2-year period. Markers of neurodegeneration were significantly reduced in the 225-mg gantenerumab group compared with placebo over 2 years, with greater relative reduction in p-tau relative to t-tau. The greatest effect was reduction in p-tau in the 225-mg gantenerumab arm at 2 years relative to the change in the placebo arm. There was no treatment effect on CSF $A\beta_{1-42}$ (Nikolcheva et al. 2015). Because no evidence of efficacy was demonstrated with these therapies in clinical trials *yet,* changes in these biomarkers *provide meaningful information about the pharmacodynamic effects of gantenerumab and the effect on* pathologic processes underlying AD.

Based on these data and on the proposed mechanism of action of gantenerumab, levels of CSF t-tau and p-tau *and additional exploratory biomarkers reflecting neurodegeneration* will be assessed at baseline and following treatment. Because gantenerumab is expected to clear amyloid from the brain, levels of CSF $A\beta_{1-42}$ will also be measured.

3.3.8.2 Positron Emission Tomography

The definitive diagnosis of AD requires the presence of progressive dementia during life and the postmortem presence of neuropathological lesions (i.e., neuritic plaques composed of β-amyloid aggregates and neurofibrillary tangles formed from hyperphosphorylated tau protein). However, imaging approaches using ligands that demonstrate high affinity for aggregated amyloid are able to provide an assessment of deposition in vivo, which can be evaluated over time (Clark et al. 2011).

3.3.8.3 Brain Volumetry, Connectivity, and Fiber Tract Integrity

A characteristic feature of AD is neuronal destruction. Such neuronal loss is demonstrated at a macroscopic level by progressive cerebral atrophy, which can be tracked on MRI (Fox and Kennedy 2009). Multiple changes in brain anatomy beyond those associated with normal aging have been reported in patients with AD (e.g., enlarged ventricles, decreased cortical thickness, decreased total brain volume, and hippocampal atrophy), and there is evidence for strong correlations between these imaging biomarkers and functional cognitive measures (Li and Wahlund 2011). Based on volumetric MRI measurements, the two most established markers of disease

progression in longitudinal observational studies are hippocampal and whole brain atrophy (Fox et al. 2000, 2005; Jack et al. 2010), with ventricular expansion a related quantitative marker.

Therefore, to quantify the effects of gantenerumab on neurodegeneration, whole brain volume, ventricular enlargement, and regional brain volume changes will be assessed at screening and following treatment. All MRI reads and volume measures will be conducted by the central reader.

In addition to the structural brain volume changes, changes in brain functioning of patients will be assessed using a blood oxygenation level-dependent (BOLD) resting-state functional MRI (rs-fMRI) procedure (at sites where this procedure is available) with a paradigm-free procedure (Grecius et al. 2004; Filippi and Agosta 2011). Increased concentrations of Aβ in the brains of patients with AD contribute to neuronal degeneration in the brain over time and have been associated with reduced functional connectivity of various brain networks using rs-fMRI (Sheline et al. 2010; Binnewijzend et al. 2012; Brier et al. 2012; Sheline and Raichle 2013). Resting-state functional connectivity has been found to be decreased in brain regions such as the hippocampus, the default mode network (regions such as precuneus, anterior cingulate, and parietal and temporal cortices), and cortical regions in which the functional connectivity is continuously decreased as disease progresses. It has also been found to be decreased in cognitively normal elderly patients with brain amyloid deposition (PiB+PET scans). Alteration of the decreased brain functional connectivity has been shown using therapeutic interventions such as memantine (Lorenzi et al. 2011) or donepezil in patients with AD (Goveas et al. 2011; Solé-Padullés et al. 2013). Increased brain functional connectivity was found already after 3 months of treatment with donepezil, which correlated with changes in cognitive measures such as the ADAS-Cog (Goveas et al. 2011; Solé-Padullés et al. 2013). Therefore, therapeutic interventions, which act to remove Aβ from the brains of patients with AD, may help to reverse the altered functional connectivity presumably caused by the accumulation of Aβ in the brain.

The integrity of white matter tracts will be assessed prior to and after treatment with gantenerumab using diffuse tensor imaging (DTI)-MRI techniques. DTI-MRI is based on the measurement of diffusion properties of water molecules in the axonal fiber tracts in white matter. Whereas water molecules can diffuse isotropically in CSF, they are restricted axially in white matter bundles. Widespread group differences in the degree of anisotropic diffusion, or fractional anisotropy (FA), has been seen between patients with AD and healthy subjects (Jack et al. 2015). Greater FA values are thought to indicate greater white matter integrity. Likewise, mean diffusivity, which measures the average rate of diffusion in all directions, has been shown to be higher in AD groups compared with healthy controls, presumably owing to increased white matter injury in patients with AD (Nir et al. 2013).

At sites having the required software and hardware, rs-fMRI (BOLD rs-fMRI) and DTI-MRI will be performed when feasible during the same scanning session as the structural MRI to assess functional brain connectivity and fiber tract integrity before and after treatment with gantenerumab.

4. MATERIALS AND METHODS

4.1 PATIENTS

This study will enroll approximately *760* patients with increased brain amyloid burden (defined according to CSF or PET criteria), objective memory impairment indicated by cognitive assessment, and a diagnosis of probable AD or prodromal AD based on relevant NIA/AA criteria during the global enrollment phase. Additional criteria are defined in Sections 4.1.1 and 4.1.2.

An increase in sample size may be considered in the event of changes to the sample size assumptions on the basis of blinded data review or factors external to the study.

If at least 1 patient is enrolled *at sites* in *mainland* China*, Hong Kong, and Taiwan that are recognized by the CFDA* during the global enrollment phase, additional patients may be enrolled in a China extension to ensure a *total enrollment that is* sufficient *to support* registration in China. All patients enrolled *at CFDA-recognized sites* in the global enrollment phase will be included in the primary analysis.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Ability to provide written consent signed by the patient (co-signed by the patient's legally authorized representative, if required by the local regulations, guidelines, and independent Ethics Committee [EC] or Institutional Review Board [IRB])
- Age 50–90 years old at screening, inclusive
- Availability of a person (referred to as the "study partner" throughout this protocol) who:
  - *Agrees to participate throughout the 2 years duration of study*
  - *In the investigator's judgment,* has frequent and sufficient contact (e.g., 5 times per week or approximately 10 hours per week) with the patient
  - *In the investigator's judgment, is* able to provide accurate information regarding the patient's cognitive and functional abilities, *including knowledge about domestic activities, hobbies, routines, social skills, and basic activities of daily life; work and educational history; cognitive performance including memory abilities, language abilities, temporal and spatial orientation, judgment and problem solving; emotional and psychological state; and can report any changes in the general health status*
  - Agrees to provide information *and to complete all aspects of the study* at clinic visits (which require partner input for scale completion)

  - Signs the necessary Informed Consent Form(s), and has sufficient cognitive capacity to accurately report on the patient's behavior *as well as* cognitive and functional abilities
  - Is *fluent* in *the language used at the site and has* sufficiently good general health to have a high likelihood of maintaining the same level of interaction with the patient and participation in study procedures throughout the duration of the study

    Every effort should be made to have same study partner participate throughout the duration of the study.
- Fluency in the language of the tests used at the study site
- Willingness and ability to complete all aspects of the study (including MRI, lumbar puncture [if applicable], clinical genotyping, and PET imaging [if applicable])

  The patient should be capable of completing assessments either alone or with the help of the study partner.
- Adequate visual and auditory acuity, in the investigator's judgment, sufficient to perform the neuropsychological testing (eye glasses and hearing aids are permitted)
- Evidence of AD pathological process, as confirmed by CSF tau/$A\beta_{42}$ or on amyloid PET scan by qualitative read by the core/central PET laboratory
- Demonstrated abnormal memory function at screening (FCSRT cueing index ≤ 0.67 and free recall ≤ 27)
- Screening MMSE score ≥ 22 and CDR-GS of 0.5 or 1.0
- Probable AD dementia (consistent with NIA/AA core clinical criteria for probable AD dementia) (McKhann et al. 2011) or prodromal AD (consistent with the NIA/AA diagnostic criteria and guidelines for mild cognitive decline due to AD) (Albert et al. 2011)
- If the patient is receiving symptomatic AD medications, a stable dosing regimen for at least 3 months prior to baseline and until randomization
- Agreement not to donate blood or blood products for transfusion for the duration of the study and for 1 year after final dose of study drug
- Agreement not to participate in other research studies for the duration of this trial and its associated substudies
- For enrollment in the China extension, *patients must have residence in mainland China, Hong Kong, or Taiwan and be of Chinese ancestry.*
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least *16* weeks after the last dose of study drug

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

4.1.2.1 Exclusions Related to Central Nervous System Disorders

Patients who meet any of the following criteria related to CNS disorders will be excluded from study entry:

- Any evidence of a condition other than AD that may affect cognition, including, but not limited to, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, *Parkinson* disease, corticobasal *syndrome*, Creutzfeldt-Jakob disease, progressive supranuclear palsy, frontotemporal *lobar* degeneration, Huntington disease, normal pressure hydrocephalus, seizure disorder, delirium or hypoxia
- History or presence of clinically evident *systemic* vascular disease (e.g., clinically significant carotid/vertebral *artery* stenosis or plaque, aortic aneurysm*),* that in the opinion of the investigator has the potential to affect cognitive function
- *History or presence of clinically evident cerebrovascular disease (e.g., intracranial or cerebral vascular malformations, aneurysm, intracranial macrohemorrhage)*

  Patients with asymptomatic developmental venous anomalies may be eligible after discussion with and approval by the Medical Monitor.
- *History or presence of posterior reversible encephalopathy syndrome*
- History or presence of any stroke with clinical symptoms within the past 12 months, or documented history within the last 6 months of an acute event that is consistent, in the opinion of the investigator, with a transient ischemic attack
- History of severe, clinically significant (persistent neurologic deficit or structural brain damage) CNS trauma (e.g., cerebral contusion)
- History or presence of intracranial mass (e.g., glioma, meningioma) that could potentially impair cognition
- Presence of infections that affect brain function or history of infections that resulted in neurologic sequelae (e.g., HIV, syphilis, neuroborreliosis, and viral or bacterial meningitis and encephalitis)
- History or presence of systemic autoimmune disorders that potentially cause progressive neurologic disease with associated cognitive deficits (e.g., multiple sclerosis, lupus erythematosus, anti–phospholipid antibody syndrome, and Behçet disease)

- History of schizophrenia, schizoaffective disorder, major depression, or bipolar disorder

  History of major depression is acceptable if patient has had no episode within the past year or is considered in remission or depression is controlled by treatment.
- At risk *for* suicide in the opinion of the investigator
- Alcohol and/or substance abuse or dependence (according to the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, Version 5) within the past 2 years

  Nicotine use is allowed.

  Marijuana use is not allowed and must be discontinued at least 3 months before screening.

4.1.2.2 Imaging-Related Criteria

Patients who meet any of the following imaging criteria will be excluded from study entry:

- According to the MRI central reader, MRI evidence of any of the following:
  - >2 lacunar infarcts
  - Any territorial infarct >1 cm^3
  - Any white matter lesion that corresponds to an overall Fazekas score of 3 that requires at least one confluent hyperintense lesion on the fluid-attenuated inversion recovery (FLAIR) sequence, which is ≥ 20 mm in any dimension
- Combined number of microbleeds and areas of leptomeningeal hemosiderosis (i.e., cumulative ARIA-H) on MRI more than five (and should not include any disseminated leptomeningeal hemosiderosis) based on the review performed by the central reader prior to randomization
- Presence of any other significant cerebral abnormalities, including ARIA-E, as assessed on MRI
- Inability to tolerate MRI procedures or contraindication to MRI, including, but not limited to, presence of pacemakers not compatible with MRI, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan, or any other clinical history or examination finding that, in the judgment of the investigator, would pose a potential hazard in combination with MRI

4.1.2.3 Cardiovascular Disorders

Patients who meet any of the following criteria related to cardiovascular disorders will be excluded from study entry:

- History or presence of clinically symptomatic atrial fibrillation requiring maintenance therapy

  Patients who experienced non-valvular atrial fibrillation that resolved more than 1 year ago and was not associated with prior stroke are eligible.

- Within the last year, unstable or clinically significant cardiovascular disease (e.g., myocardial infarction)

  Heart failure classified as New York Heart Association Class *I* or *II* cardiac disease *is allowed if not associated with hospitalization within the previous 12 months.*

- Uncontrolled hypertension (e.g., blood pressure generally $>$160 mmHg systolic or $>$95 mmHg diastolic)

4.1.2.4 Hepatic and Renal Disorders

Patients who meet any of the following criteria related to hepatic and renal disorders will be excluded from study entry:

- Chronic kidney disease, indicated by creatinine clearance $<$30 mL/min to be calculated by the central laboratory using the Cockcroft-Gault formula at screening, which remains $<$30 mL/min if retested
- Confirmed and unexplained impaired hepatic function as indicated by screening AST or ALT $\geq 3\times$ the upper limit of normal (ULN) or total bilirubin $\geq 2\times$ ULN

4.1.2.5 Infections and Immune Disorders

Patients who meet any of the following criteria related to infections and immune disorders will be excluded from study entry:

- History of, or known to currently have HIV infection, or hepatitis B or hepatitis C infection that has not been adequately treated in the opinion of the investigator, or history of spirochete infection of the CNS (e.g., syphilis, Lyme disease, or borreliosis)
- Systemically, clinically significantly immunocompromised patients, owing to continuing effects of immune-suppressing medication

4.1.2.6 Metabolic and Endocrine Disorders

Patients who meet any of the following criteria related to metabolic and endocrine disorders will be excluded from study entry:

- Abnormal thyroid function as indicated by abnormal screening tests that are judged to be clinically significant by the investigator, or abnormal thyroid function that requires a new treatment or an adjustment of current treatment

  A patient may be rescreened if there is no improvement in cognition in the investigator's judgment after 3 months of adequate treatment for thyroid function.

- *Patients with evidence of folic acid deficiency (as indicated by folic acid level below the lower limit of normal) or vitamin B-12 deficiency (as indicated by vitamin B-12 level below the lower limit of normal and/or methylmalonic acid levels above ULN)*

  A patient may be rescreened if there is no improvement in cognition after 3 months of adequate treatment for folic acid or vitamin B-12 deficiency.

- Screening hemoglobin A_{1c} (HbA_{1C}) > 8% (retesting is permitted if slightly elevated) or poorly controlled insulin-dependent diabetes (including hypoglycemic episodes)

  A patient may be rescreened after 3 months to allow optimization of diabetic control.

4.1.2.7 Exclusions Related to Medications

The following medications are prohibited for a pre-specified duration prior to study start, as indicated, and during the entire period of study participation (Patients who start these medications during the study may be withdrawn from study treatment*; for additional details on prohibited medications, please refer to Appendix 7*):

- Any previous administration of gantenerumab or active immunotherapy (vaccine) that is being evaluated to prevent or postpone cognitive decline
- Any passive immunotherapy (immunoglobulin) or other long–acting biologic agent that is under evaluation to prevent or postpone cognitive decline within 1 year of screening
- Any other investigational treatment or any other treatment with a monoclonal antibody within 5 half-lives or 4 months prior to screening, whichever is longer
- Any previous treatment with medications specifically intended to treat Parkinson symptoms or any other neurodegenerative disorder within 1 year of screening and with no *plans to initiate such medications* prior to randomization

  Certain medications are acceptable if the patient is taking the medicine for a non-neurodegenerative disorder, such as restless leg disorder (e.g., pramipexole).
- Typical antipsychotic or neuroleptic medication within 6 months of screening and with no planned changes prior to randomization except as brief treatment for a non-psychiatric indication (e.g., emesis)

  Atypical antipsychotic medications are not allowed except for intermittent short-term use and will need to be discontinued 2 days or *at least* 5 half-lives (whichever is longer) prior to any neurocognitive assessment.
- Anti-coagulation medications within 3 months of screening with no *plans to initiate any* prior *to* randomization

  Anti-platelet treatments (e.g., aspirin, clopidogrel, and dipyridamol) are permitted.

  Short-term, perioperative use of anticoagulant medications will not result in permanent discontinuation from the study; however, any such use must be discussed prospectively with the Medical Monitor and may require temporary study drug interruption.
- Chronic use of opiates or opioids (including long-acting opioid medication) within 3 months of screening with no *plans to initiate any* prior *to* randomization

  Intermittent short-term use of short–acting opioid medications for pain is permitted except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

- Stimulant medications (amphetamine, methylphenidate preparations, or modafinil) within 1 month of screening and throughout the study
- Chronic use of benzodiazepines, barbiturates, or hypnotics from 3 months before screening and with no *plans to initiate any* prior *to* randomization

  Intermittent short-term use of benzodiazepines, buspirone, or short-acting hypnotic medication for sleep or anxiety is allowed except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

4.1.2.8 Other Exclusions

Patients who meet any of the following criteria will be excluded from study entry:

- Other causes of intellectual disability that may account for cognitive deficits observed at screening (e.g., static encephalopathy, closed brain injury, mental retardation)

  This may be based on, for example, patient's sufficient education or work experience.
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study
- Deformity of the lumbosacral region of the spine that in the opinion of the investigator would contraindicate lumbar puncture in patients who will have lumbar puncture
- Clinically significant abnormal screening blood, CSF (if applicable), or urine results that remain abnormal at retest
- Impaired coagulation (screening prothrombin time [PT] $> 1.2\times$ the ULN that remains abnormal on retest)
- History of cancer, with the following exceptions:
  - If considered to be cured
  - If not being actively treated with anti-cancer therapy or radiotherapy and, in the opinion of the investigator, is not likely to require treatment in the ensuing 5 years
  - For prostate cancer or basal cell carcinoma, no significant progression over the previous 2 years
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins, including gantenerumab
- Hypersensitivity to any of gantenerumab excipients
- Any other severe or unstable medical condition that, in the opinion of the investigator or Sponsor, could be expected to progress, recur, or change to such an extent that it could put the patient at special risk, bias the assessment of the clinical or mental status of the patient to a significant degree, interfere with the patient's ability to complete the study assessments, or would require the equivalent of institutional or hospital care

- Residence in a skilled nursing facility such as a convalescent home or long-term care facility: Patients who subsequently require residence in such facilities during the study may continue in the study and be followed for efficacy and safety, provided that they have a study partner who meets the minimum requirement

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Randomization will be performed centrally using an interactive voice or Web-based response system (IxRS). After screening, patients who meet all eligibility criteria will be randomly assigned to one of two treatment groups (gantenerumab or placebo). The ratio will be 1:1, one active to one placebo. The randomization method will be stratified block-randomization. Randomization to treatment allocation will be stratified by geographic region *(Western Europe vs. Rest of the World vs. North America)*, patient *APOE* ε4 status (carrier vs. non-carrier), patient stage of disease (prodromal vs. mild AD), use of AD medication (present vs. absent), and participation in the longitudinal amyloid *and tau* PET *substudies*. Except in circumstances in which a health authority, EC, or IRB requires it, a patient will not be told of his or her *APOE* ε4 status. Individual patient *APOE* ε4 genotype results will be blinded to patients, investigators, and the Sponsor. *APOE* ε4 status information will be supplied directly to the IxRS vendor by the central testing laboratory so that the information can be incorporated at the time of randomization. For patients for whom *APOE* ε4 status is already known, the results will be blinded to the Sponsor and as much as possible to the site and central MRI reader.

The study is to be conducted in a double-blind manner to minimize potential bias from investigators and patients. The Sponsor will be blinded to study treatment. The Master Randomization or Master Medication List will not be available at the study center, to Roche monitors, Roche project statisticians, or to the project team at Roche. Unblinding should not occur except in the case of emergency situations where knowledge of the study drug assigned would affect patient *care*. The investigator should make every effort to contact Roche before unblinding a patient. In the event that the investigator unblinds a patient without prior notification, the investigator must contact Roche within 1 working day of the event. Any request from the investigator for information about the treatment administered to study patients for another purpose must be discussed with the Medical Monitor.

If unblinding is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the investigator wants to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event).

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.2.2) that are considered by the investigator or Sponsor to be related to study drug.

4.3 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is gantenerumab.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Gantenerumab and Placebo

Gantenerumab and placebo will be supplied by the Sponsor as *liquid formulation* ready for SC administration. Packaging of the study drug will be overseen by the Roche Clinical Trial Supplies Department and will bear a label with the identification required by local law, the protocol number, study drug identification, and dose. The packaging and labeling will be in accordance with Roche standard and local regulations. Upon receipt of the investigational products at the site, site personnel should check the product for damage and verify the proper identity, quantity, and integrity of the study drug. Site personnel should report any deviations or product complaints to the monitor upon discovery. For further details, please refer to the Gantenerumab Investigator's Brochure.

For information on the formulation and handling of gantenerumab, see the pharmacy manual and Gantenerumab Investigator's Brochure.

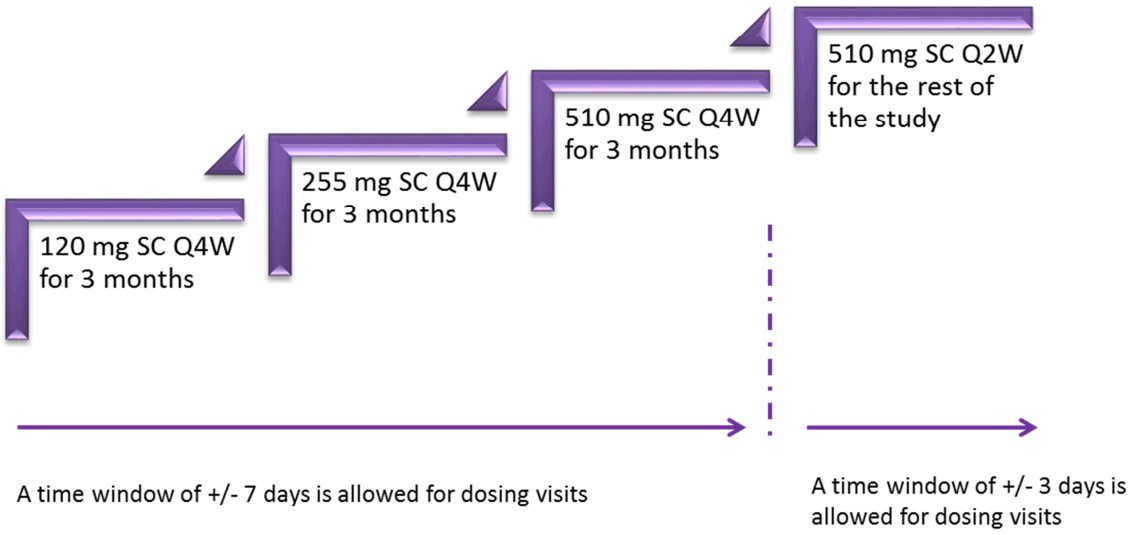
4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Gantenerumab and Placebo

Gantenerumab or placebo will be administered by SC injection to all patients.

Gantenerumab will be administered by SC injection to all patients randomized to the active treatment arm, regardless of *APOE* ε4 status, at a dose of *120* mg SC Q4W for 3 months, *255* mg SC Q4W for 3 months, and *510* mg SC Q4W for 3 months, prior to reaching *the target dose* (see Figure 6). Once the target dose is reached, study drug will be administered *every 2 weeks (Q2W administration of 510 mg SC gantenerumab)*. The switch to a Q2W administration schedule allows decreasing the number of SC administrations in the abdomen per visit.

Figure 6 Overall Gantenerumab Dosing Design



Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous.

For Q4W injections, a time window of ±7 days is allowed for dosing visits. Once study drug is administered Q2W, the time window for dosing visits is ±3 days.

Regardless of dose, each patient will undergo up to a total of 43 dosing visits in the study. Injections will be administered as one 0.8-mL (120-mg dose), one 1.7-mL (255-mg dose), or two 1.7-mL injections (510-mg dose) subcutaneously to the abdomen, respectively.

Placebo of identical composition (except protein) and identical volume to gantenerumab will be administered by SC injection to all patients randomized to placebo at the same frequency and using the same route of administration.

On study drug administration days that include efficacy assessments (see the schedule of activities in Appendix 1), study drug must be administered at the clinical site. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

At applicable sites, study drug may be administered by a trained nursing professional at the patient's home or another suitable location, if the patient has given written informed consent to participate in home nursing visits.

Rules for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.3.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.2.2 *PET Tracers*

All patients who are enrolled in PET substudies will be assessed by PET imaging using an appropriate PET ligand. For screening, the possible amyloid PET ligands will be florbetapir, florbetaben, and flutemetamol. *According to E.U. guidance, the PET tracers used in the context of this study have been designated as non-IMP. In some regions, according to local regulations, these PET tracers may be considered to be IMP.*

In countries where the PET radioligands are approved for marketing, the approved local product information will be provided, and in countries where they are not approved for marketing, the Investigator's Brochures will be provided.

Details about the PET substudies are described in separate protocols.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (gantenerumab or placebo) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to Gantenerumab

The Sponsor will offer continued access to Sponsor study drug (gantenerumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Sponsor study drug (gantenerumab) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Sponsor study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient

- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Sponsor study drug (gantenerumab) after completing the study if any of the following conditions are met:

- The Sponsor study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the drug or data suggest that the drug is not effective for AD
- The Sponsor has reasonable safety concerns regarding the drug as treatment for AD
- Provision of the drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

All eligible patients will be offered to receive gantenerumab as part of an extension study, as described in Section 3.1.

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 3 months prior to screening to the study completion or discontinuation visit. All such medications (including name, dose, administration schedule, start and end dates) should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients are eligible for study participation whether or not they are receiving approved medication for AD (i.e., *acetylcholinesterase inhibitors,* memantine, *and/*or medical food supplement*s*, where approved). Information about background AD medication (e.g., drug name, dose, and start and stop dates, reason for interruption or modification) has to be captured on eCRF. Randomization will be stratified for patients taking and not taking approved anti-dementia medications.

Adding a new medication or changing the dose of a medication after randomization should occur only for the treatment of an adverse event or in case of AD progression. Whenever possible, a medication listed below should be used if appropriate.

The following medications are permitted if the dose and dose regimen have been stable for at least 3 months prior to screening and are expected to remain stable after screening or if required for treatment of an adverse event after randomization:

- Anticonvulsant medications for an approved pain indication
- Selective serotonin reuptake inhibitors for the treatment of depressive symptoms
- Over-the-counter and/or herbal medications, food additive, or any other agent or supplement intended to improve cognition or reduce cognitive decline
- Medications used to treat a mood or anxiety disorder given as maintenance treatment *(with the exception of benzodiazepine)*
- Intermittent use of short-acting (non-extended release) opioid medications for pain except within 2 days or 5 half-lives (whichever is the longer) of any cognitive assessment (up to a maximum of 3 consecutive days per month)
- Intermittent use of benzodiazepines, including alprazolam, lorazepam, oxazepam, triazolam, or temazepam, or a one-time dose of diazepam or a short–acting hypnotic medication (e.g., zolpidem) if use is intermittent for sleep or anxiety, except *within* 2 days or 5 half-lives (whichever is the longer) prior to any cognitive assessment
- A dose of benzodiazepine for pre-surgical and pre-imaging sedation at appropriate visits if allowed by the EC or IRB
- Intermittent use of centrally acting antihistamine medications except *within* 2 days or 5 half-lives (whichever is the longer) prior to any cognitive assessment
- Under certain circumstances, initiation of anti-hemostasis medications during the study conduct

  Anticoagulation therapy lasting no longer than 3 weeks (e.g., temporary usage during surgery) is permitted. Nevertheless, no anticoagulation therapy should be initiated without discussion with and approval by the Medical Monitor.

Concomitant and excluded therapies for determination of patient eligibility are described in Section 4.1.2.7.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

4.4.2 Prohibited Therapy

Any medication that is prohibited before screening is also prohibited during conduct of the study (see Section 4.1.2.7). If a patient receives any prohibited treatment during the study, the patient may be withdrawn from study treatment.

4.5 STUDY ASSESSMENTS

Refer to Appendix 1 for the schedule of activities to be performed during the study.

At applicable sites, certain study assessments may be performed by a home nursing (HN) professional at the patient's home or nursing center to improve access and convenience for patients participating in the study. The Sponsor will select a healthcare company that will be responsible for providing HN services for participating sites (the HN vendor). The HN vendor is responsible for ensuring that all HN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that HN services are appropriate for a patient and the patient gives written informed consent to participate in HN visits, the HN network will communicate with the patient and the patient's site. HN visits will be scheduled on specified visit days to allow relevant assessments to be performed by the HN professional. The schedule of activities (see Appendix 1) specifies which assessments may be performed by an HN professional.

4.5.1 Informed Consent Forms and Screening Log

All patients and study partners must review, sign, and date the most current IRB/EC-approved written informed consent for participation in the study before any study-specific prescreening assessments, screening tests or evaluation are performed. Informed Consent Forms for enrolled patients and their study partners and for those who are not subsequently enrolled will be maintained at the study site.

All prescreening and screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients prescreened and screened and to confirm eligibility or record reasons for screening failure, as applicable. Prescreening is optional and is covered by a dedicated Informed Consent Form.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), smoking history, use of alcohol, and drugs of abuse. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 3 months prior to screening visit will be recorded. Demographic data will include age, sex, and self-reported race/ethnicity. Medical history and demographic data will be collected at the screening visit only.

As this study is being conducted in multiple geographic regions, it is likely that patients of different ethnic origins will be enrolled in the study. Although there is currently no indication that gantenerumab is metabolized or eliminated differently or that the

treatment effect would be different in patients of different ethnic origins, collecting this information is essential to adequately evaluate the results of this study (e.g., possible differences in PK exposure [concentration of the drug in the blood] or treatment effect).

4.5.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

The schedule of activities indicates when complete physical examinations (including neurological systems) are to be recorded (see Appendix 1, Tables 1 and 2).

Limited, symptom-directed physical examinations should be performed per the schedule of activities (or as clinically indicated). Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

In addition, weight will be obtained at screening, at the Week 104 or early termination visit, and at any other visit as deemed necessary by the investigator. *Height will be obtained at screening only.*

4.5.4 Vital Signs

Vital signs will include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the patient is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements.

Pulse rate will be determined by radial pulse and will be recorded as beats per minute. The pulse rate should be counted for a minimum of 20 seconds at each assessment.

Vital sign measurements may be performed by an HN professional.

The schedule of activities indicates when vital signs (blood pressure and pulse rate) are to be recorded (see Appendix 1).

4.5.5 Cognitive, Functional, and Health Economics Assessments

The assessments described in this section will be performed as outlined in the schedule of activities (see Appendix 1) and in the order specified in Section 4.6.

Whenever possible, there should be consistency in the rater and study partner who complete the scales for each patient throughout the duration of the study. Potential raters will receive training and be approved by the rating scale contract research organization (CRO) prior to being allowed to administer any cognitive assessments or rating scales in the study.

Given that the primary outcome measure in this trial involves subjective judgment, the adequacy of patient and study partner interviews and ratings will be monitored by an endpoint reliability program administered by the rating scale vendor; this is considered an essential part of good research methodology. For the primary endpoint as well as for some other scales, audio recordings may be used for quality assurance purposes. Prior studies have clearly demonstrated that the failure to adequately monitor such ratings can substantially increase the risks of failed trials (Becker and Greig 2008; Kobak 2010).

4.5.5.1 Clinical Dementia Rating Scale

The CDR global score (CDR-GS) *characterizes a patient's level of impairment according to the following categories: 0 (normal), 0.5 (very mild dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia).* The SOB score is a detailed quantitative general index that provides more information than the CDR-GS in patients with mild dementia *(Berg 1988; Morris et al. 2001, O'Bryant et al. 2010) and is scored from 0–18 with higher scores indicating greater impairment.* The CDR characterizes six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The necessary information to make each rating is obtained through a semi-structured interview with the patient and a reliable informant or collateral source (e.g., a study partner).

As much as is feasible, the CDR should be administered to an individual patient by the same assessor throughout the study and that assessor should not perform the MMSE, ADAS-Cog, *Verbal Fluency Task, Coding,* FAQ, or Alzheimer's Disease Cooperative Study Group–Activities of Daily Living (ADCS-ADL). However, if in exceptional circumstances only this assessor is available to perform these other scales, then the CDR patient interview must be completed after the study partner interview but before ADAS-Cog, MMSE, *Verbal Fluency Task, Coding, and other scales are completed. Nevertheless, at screening, baseline, and Week 104, the CDR rater cannot perform other scales than the CDR. In addition, the CDR rater should not be involved in safety assessments and especially should not receive information about any ARIA findings.*

4.5.5.2 Alzheimer's Disease Assessment Scale–Cognitive Subscale

The ADAS-Cog is the most frequently used scale to assess cognition in clinical trials for mild to moderate AD dementia (Rozzini et al. 2007; Connor and Sabbagh 2008; Ihl et al. 2012). More specifically, the ADAS-Cog is a patient-based assessment that measures learning and memory, language production, language comprehension, constructional praxis, ideational praxis, and orientation. The modified version will be used; it has 13 items and includes the addition of delayed word recall and a number of cancellation

subtests, as well as use of only one trial for word recognition (Mohs et al. 1997). Equivalent alternate forms of the word recall, word recognition, and number cancellation subtests will be used in successive test administrations.

4.5.5.3 Mini-Mental State Examination

The MMSE is a set of standardized questions used to evaluate possible cognitive impairment and help stage the severity level of this impairment (Folstein et al. 1975). The questions target six areas: orientation, registration, attention, short-term recall, language, and constructional praxis/visuospatial abilities. The MMSE is a patient-based assessment.

4.5.5.4 Free and Cued Selective Reminding Test–Immediate Recall

The FCSRT-Immediate Recall (FCSRT-IR) is a patient-based assessment that measures memory under conditions that control attention and cognitive processing. Impairments in FCSRT-IR performance have been associated with preclinical and early dementia in several longitudinal epidemiological studies (Grober and Buschke 1987; Sarazin et al. 2007). The 16-word version of the test will be used in this study.

4.5.5.5 Verbal Fluency Task

The category verbal fluency (e.g., animals) is a patient-based assessment that measures speed and flexibility of verbal thought. Verbal fluency tests are sensitive tools for detecting dementia (Pasquier et al. 1995; Lezak et al. 2004) and for monitoring decline over time (Clark et al. 2009).

4.5.5.6 *Coding*

The Coding, also called Digit Symbol Substitution Test (or DSST), is a subtest from the Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV; Wechsler 2008). The Coding is a patient-based assessment that measures speed of processing and associative memory. The test is known to be sensitive to disease progression (Lezak et al. 2004). The 120-second version of the test will be used in this study.

4.5.5.7 Functional Activities Questionnaire

The FAQ (Pfeffer et al. 1982) is an informant-based measure of functional abilities. Informants provide performance ratings of the target person on ten complex higher-order activities.

4.5.5.8 Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory

The ADCS-ADL (Galasko et al. 1997) is the scale most widely used to assess functional outcome in patients with AD (Vellas et al. 2008). The ADCS-ADL is a 23-item informant-based questionnaire that covers both basic activities of daily living (ADL) (e.g., eating and toileting) and more complex ADL or instrumental ADL (e.g., using the telephone, managing finances, preparing a meal). *It has a 4-week recall period. Total scores range from 0–78, with higher scores indicating better functioning.*

4.5.5.9 Zarit Caregiver Interview–Alzheimer's Disease

The Zarit Caregiver Interview–Alzheimer's Disease (ZCI-AD) is a modified version of the Zarit Burden Interview, which was originally designed to reflect the stresses experienced by caregivers for people with dementia (Zarit and Zarit 1990). The modified version includes slight modifications in item and title wording (e.g., removal of "your relative" to refer directly to the patient, removal of "burden" from title) and the use of 11-point numerical rating scales. The ZCI-AD scale consists of 30 items and is completed by the study partner without involvement from the site staff. *It has a 4-week recall period.*

If a patient's study partner is replaced during the study, the ZCI-AD will not be completed by his or her new study partner.

4.5.5.10 Quality of Life–Alzheimer's Disease

The Quality of Life–Alzheimer's Disease (QoL-AD) was developed to assess QoL in patients who have dementia (Logsdon et al. 1999, 2002). The QoL-AD consists of 13 items covering aspects of patients' relationships with friends and family, physical condition, mood, concerns about finances, and overall assessment of QoL. *The total score is the sum of the 13 items and ranges from 13–52, with higher scores indicating better HRQOL.*

In this study, the QoL-AD will be administered in a standardized, structured interview format to patients by investigative staff in order to gather patient responses about QoL. The study partner will also complete the study partner version of the questionnaire to enable proxy responses from the study partner.

4.5.5.11 EQ-5D

The EuroQoL–Five Dimensions (EQ-5D) is a standardized measure of health status designed to provide a simple generic measure of health for clinical and economic appraisal. It is broadly applicable across a wide range of health conditions and treatment.

The EQ-5D assesses five domains to provide a health state index. These are anxiety/depression, pain/discomfort, usual activities, mobility, and self-care.

The following two versions will be used in this study:

- EQ-5D-5L Proxy, Version 1: The study partner (the proxy) is asked to rate the patient's health-related QoL in his or her (the proxy's) opinion.
- EQ-5D-5L, Self-Complete Version: The study partner is asked to rate his or her own health-related QoL.

4.5.5.12 Resource Utilization in Dementia Scale

The Resource Utilization in Dementia (RUD) scale (Wimo et al. 2003) aims to document formal and informal resource use in a clinical trial setting. The RUD-Lite captures the most important elements in dementia care: accommodation, informal care,

hospitalizations, and community care services. Information on study partner sociodemographics in addition to working status and effect on productivity will be collected. The amount of informal care will be collected according to three types of care: personal ADL, instrumental ADL, and supervision. Data on accommodation and temporary changes in accommodation during the last month and the duration of these will be collected according to four levels of accommodation: own home, intermediate forms of accommodation, dementia-specific residential accommodation, and nursing home. Resource utilization will be recorded as the number of nights spent in different types of hospital wards, the number of visits to the most common types of outpatient care, and the number of visits in community care services.

4.5.5.13 Neuropsychiatric Inventory Questionnaire

The Neuropsychiatric Inventory–Questionnaire (NPI-Q) (Kaufer et al. 2000) was developed to assess a wide range of behaviors encountered in dementia patients, to provide a means of distinguishing severity of behavioral changes, and to facilitate rapid behavioral assessment through the use of screening questions. It is an informant-based instrument in which 12 behavioral domains are evaluated. *The recall period is the past month, and severity scores range from 0–36, with higher scores indicating greater severity.* The study partner's distress portion of the scale will not be used in this study.

4.5.5.14 Electronic Assessment of Rating Scales

The following rating scales will be captured electronically and transferred to the database directly from the core laboratory: ADAS-Cog, Verbal Fluency Task, ADCS-ADL, CDR, MMSE, FCSRT, FAQ, AD QoL, EQ-5D, RUD-Lite, NPI-Q, and CSSR-S.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

4.5.6.1 Standard Laboratory Samples

Samples for the following laboratory tests will be sent to a central laboratory for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

- Serum chemistry: AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory)

  HbA_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed according to the schedule of activities.
- Hematology: hemoglobin, hematocrit, RBC count (with morphology), WBC count, platelets, basophils, eosinophils, lymphocytes, monocytes, neutrophils, and WBC–other total counts
- Screening serology: HIV, hepatitis B, and hepatitis C
- Coagulation: PT

- Urine for drugs of abuse: At screening only, urine samples will be analyzed for the presence of the following drugs: amphetamine, benzodiazepines, cannabinoids, opiates, cocaine, barbiturates, and methadone. Results will be used to verify patient eligibility pertaining to drugs of abuse. Inconclusive results may be repeated once during the screening period. Investigators should use their best clinical judgment in cases where results may be erroneous (e.g., permitted use of opiates or ingestion of food/food supplements).
- Urinalysis: At screening only, urinalysis will be performed at the site by dipstick for blood, protein, glucose, and pH. Microscopic examination will be performed by the central laboratory if blood and/or protein results are positive or strongly positive.
- Urine for pregnancy test: Urine pregnancy testing will be performed at each dosing visit (prior to dose administration) for women of childbearing potential (including those who have had a tubal ligation), and at the site for any other female participants if required by local regulations. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory.

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

4.5.6.2 Biomarker Sampling

Samples will be obtained from all patients and will be used for research purposes to identify dynamic biomarkers that may be predictive of response to treatment with gantenerumab (in terms of dose, safety, and tolerability) and will help to better understand the pathogenesis, course, and outcome of AD and related diseases.

For patients who consent to the optional Roche Research Biosample Repository (RBR) residual biomarker samples will be kept for future biomarker research (see Section 4.5.12).

The procedures for the collection, handling, and shipping of biomarker samples are specified in the Sample Handling and Logistic Manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.12), biomarker samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Roche may keep information about screening test results, medical history, and demographic information for all patients (including non-eligible patients) for future development of diagnostic tests related to Aβ, *APOE* genotype, and AD, as well as additional analyses.

Cerebrospinal Fluid *and Serum* Sampling (for CSF-Enrolled Patients Only)

CSF samples and matching serum samples will be obtained from patients who choose to provide CSF samples during screening (CSF-enrolled patients) for confirmation of Aβ and tau levels for eligibility purposes (mandatory) and for monitoring Aβ and tau levels, as well as other CSF biomarkers at different timepoints during the study. *The matching serum samples may be used to determine parameters that allow the assessment of the blood-brain barrier status and/or inflammatory processes in the brain, such as CSF/serum albumin ratio, CSF/serum IgG and IgM indices, and oligoclonal bands. CSF and serum* samples will be collected according to the schedule of activities (see Appendix 1).Lumbar puncture will be performed by an individual who meets all local requirements and is proficient in the procedure. Lumbar puncture procedures and post–lumbar puncture care will be performed in accordance with local practice. CSF sampling should be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters. Procedures for the processing of the CSF samples can be found in the Sample Handling and Logistics Manual.

Approximately 12 mL of CSF will be collected at each timepoint. The sample will be divided into aliquots onsite and used for the following:

- Central measurement of gantenerumab levels in the CSF and biomarker analysis, including $A\beta_{1-42}$, t-tau, p-tau, as well as some exploratory markers. Samples may also be used to support the development of biomarker assays for diagnostic use.

Unused CSF samples will be kept for future biomarker research if the patient gives consent to participate in the RBR (see Section 4.5.12.5).

Clinical Genotyping

During screening, three mandatory 3-mL whole blood samples will be obtained for DNA extraction from every patient who has consented to participate in the study. All patients will be evaluated for *APOE* ε4 status, clusterin (apolipoprotein J) genotypes, and Fcγ-receptor genotype. The Fcγ-receptor genotype may play a role in PK and PD variability of antibody-based therapeutic agents and may be predictive of response and non-response.

APOE ε4 status will be determined and will be blinded to the Sponsor, investigator, and patient and will not be shared with the investigator or the patient until the study is unblinded (unless required for patient safety or by the relevant health authority or IRB/EC). Patients will have access to this information if they elect to at the end of the study. If already known, the *APOE* ε4 status will still need to be confirmed and should be kept blinded from the Sponsor. In addition, as much as possible, patient *APOE* ε4 status should remain blinded to the site and central MRI readers.

Samples and data may be used for future research or diagnostic test development.

The procedures for the collection, handling, and shipping of clinical genotyping samples are specified in the Sample Handling and Logistics Manual.

RNA Sampling

During screening and at a subsequent visit as detailed in the schedule of activities (see Appendix 1), two 2.5-mL whole blood samples will be obtained for RNA extraction from every patient who has consented to participate in the study. The sample may be used to evaluate clusterin messenger RNA and other exploratory genetic markers in peripheral blood (see Section 4.5.12).

Plasma Sampling

At *screening* and at subsequent visits as detailed in the schedule of activities (see Appendix 1), one 6-mL whole blood sample will be obtained for plasma extraction from every patient who has consented to participate in the study.

This sample will be used to evaluate exploratory plasma biomarkers in peripheral blood.

4.5.6.3 Anti-Drug Antibody Sampling

Blood samples will be collected to assess the possible development of ADAs in all patients as noted in the schedule of activities (see Appendix 1). Plasma samples will be analyzed for antibodies to gantenerumab using a bridging ELISA.

Samples collected from patients receiving placebo will not be assessed in the first instance but retained for subsequent analysis if appropriate.

Unused sample material may also be used for the purposes of current ADA assay improvement.

The procedures for the collection, handling, and shipping of PK and ADA samples are specified in the Sample Handling and Logistics Manual supplied to the site.

4.5.6.4 Pharmacokinetic Sampling

Plasma Gantenerumab Samples

Blood samples will be collected to evaluate the pharmacokinetics of gantenerumab in plasma as noted in the schedule of activities *(see Appendix 1)*.

An additional PK sample for the assessment of plasma concentrations of gantenerumab will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E, or occurrence of ARIA-H meeting discontinuation criteria.

Samples from patients receiving placebo may not be assessed at once but will be retained for subsequent analysis if appropriate. Samples will not be analyzed in real time but will be batched for analysis throughout the study.

Unused sample material may be used for the purpose of current gantenerumab assay improvement and for the quantification of specific gantenerumab glycan species.

Processing, storage, and shipping instructions for these PK blood samples are presented in a separate laboratory manual provided by the Sponsor to the clinical site.

Cerebral Spinal Fluid for Assessment of Gantenerumab Concentration (for Patients Enrolled on the Basis of CSF Criteria Only)

For patients enrolled on the basis of CSF criteria and willing to perform lumbar puncture in the schedule of activities, an aliquot of CSF obtained by lumbar puncture, described in Section 4.5.6.2, will be allocated for the measurement of gantenerumab concentration. Samples from patients receiving placebo may not be assessed at once but will be retained for subsequent analysis if appropriate.

Unused sample material may also be used for the purposes of current assay improvement.

4.5.7 Electrocardiograms

Single 12-lead ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 5 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws, brain MRI scans, and lumbar puncture). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

The following should be recorded by the electrocardiograph machine: heart rate, QRS duration, and RR, PR, and QT intervals and transferred to the *Sponsor* database from the core laboratory.

4.5.8 Columbia–Suicide Severity Rating Scale

The C-SSRS (http://www.cssrs.columbia.edu) is an assessment tool used to assess the lifetime suicidality of a patient (C-SSRS at baseline) as well as any new instances of suicidality (C-SSRS since last visit). The structured interview prompts recollection of

suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual or potential lethality. The C-SSRS baseline will be collected at baseline and the C-SSRS since the last visit will be collected at subsequent visits as indicated in the schedule of activities (see Appendix 1).

The assessment will be completed by a certified C-SSRS rater after he or she interviews the patient and the patient's study partner during the study visit.

4.5.9 Brain Magnetic Resonance Imaging

MRI should be performed using 1.5-T or 3.0-T scanners, and wherever possible the same scanner should be used for an individual patient for the full duration of the study. MRI will be conducted at patient screening for safety monitoring, as a baseline measure of structural brain volumes, and as baseline information for the PET substudies (for the schedule of activities, see Appendix 1).

Where available, exploratory MRI techniques including rs-fMRI and DTI will also be acquired. In addition, the screening MRI will be used to help determine whether the exclusion criteria are met (e.g., number of microbleeds, presence of mass lesions, etc.).

MRI will be used during the study to help assess safety such as the occurrence of microbleeds or signs potentially indicative of inflammation or ARIA-E. Additional unscheduled MRI scans may be performed to better understand relevant CNS adverse events (such as increased confusion) occurring in the context of ARIA or to follow a sign that emerges at a scheduled scan; contrast agent may be used in such a case of follow-up MRI scans if administration of contrast agent is considered safe for the patient according to local standards. In addition, structural MRI (to assess whole brain and regional brain atrophy), fMRI, and DTI-MRI will be performed at multiple timepoints to determine potential treatment effects on MRI outcome measures (according to the schedule of activities).

MRI scans will include the following sequences:

- 3D T_1-weighted gradient recalled echo (GRE) scans
- T_2*-weighted GRE scans
- T_2-weighted FLAIR scans
- BOLD rs-fMRI, if available (to assess resting-state functional connectivity at investigative sites having the required software and sequences)
- DTI-MRI, if available (to assess fiber tract integrity)

For details on the specific imaging sequences and acquisition times required, refer to the MRI Manual.

MRI should not be performed unless at least 3 days have passed since a lumbar puncture. If an MRI and lumbar puncture are both scheduled for the same day, the MRI should be performed first.

All images (except BOLD fMRI and DTI-MRI) will be used to assess MRI inclusion and exclusion criteria.

MRI scans will be reviewed by a central MRI core laboratory, which will perform the diagnostic reads and assessment of MRI outcome measures. MRI scans should preferably be transferred to the central MRI core laboratory electronically. Data transfer from individual study sites to the central MRI core laboratory may take up to 7−10 days, if not done electronically. Upon receipt of the MRI scans from the study sites, the central MRI core laboratory will provide the diagnostic reads. MRI results must be made available to investigators prior to next dosing (refer to Section *5.1.3* for additional details on MRI safety management).

MRI facility qualification and scan quality control will be performed by the central MRI core laboratory.

Additional instructions regarding the procedures for MRI scan acquisition and transmittal to the central reading facility can be found in the MRI Manual.

4.5.10 Healthy Volunteer Magnetic Resonance Imaging Scans for Site Qualification

As part of site qualification, one to two volunteers (preferably two) at each site should be recruited and scanned using the same machine and the same sequences to be used for site qualification before any patient is scanned in this study. The choice of healthy volunteers is at the discretion of the investigator and/or the imaging center, and the volunteer must provide written consent to take part in the scanning calibration. Volunteers must not have any contraindications for MRI scanning (evaluation per local procedures at the imaging site), and they will not be enrolled in the study or undergo any other assessments as part of the trial. If volunteer scans are acquired, then they will be reviewed for suitable image quality and used for qualitative comparison with additional scans with the same volunteer acquired after certain events as follows: at the time of a major upgrade to the site's scanner, any other event deemed significant enough to affect image quality, or per central reader guidance. This procedure will help ensure consistency in scanning quality over the duration of the study. Two volunteers are ideal in case one volunteer is no longer readily available for test scanning.

Additional instructions regarding the procedures for MRI facility qualification can be found in the MRI Manual.

4.5.11 Positron Emission Tomography Scan

A PET scan will be performed for confirmation of Aβ levels for eligibility purposes in patients (PET-enrolled patients). Three radioligands are be used for screening purposes: florbetapir F 18 (Amyvid™), flutemetamol F 18 (Vizamyl™), and florbetaben F 18 (Neuraceq™).

Screening PET scans must not be acquired prior, potentially exclusionary screening results are available in order to minimize radiation burden to patients. In order to allow sufficient flexibility for scheduling of the screening PET scan screening procedures (including central reading of the MRI scans) ideally should be completed within 2–3 weeks before the screening PET scan is required.

A positive PET scan using florbetapir F 18, flutemetamol F 18, or florbetaben F 18 acquired outside this study protocol may be permissible to confirm patient inclusion with Medical Monitor approval. Previously acquired PET scans must meet quality standards detailed in the PET Technical Operations Manual and must be centrally evaluated.

Detailed instructions regarding the procedures for PET scan methodology, including scanning procedures can be found in the PET Technical Operations Manual.

4.5.12 Optional Samples for Research Biosample Repository

4.5.12.1 Overview of the *Research Biosample* Repository

The RBR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be collected from retaining the residual samples remaining after the protocol-specified analysis has been performed on protocol-specified mandatory biomarker samples.

These residual samples will be retained from patients who give specific consent to participate in the optional study.

RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology

- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.12) will not be applicable at that site.

4.5.12.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to gantenerumab or AD:

- Leftover blood from Clinical Genotyping sample and clinical RNA sample, plasma biomarker sample, CSF samples and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing, or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.12.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR specimens, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.12.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.12.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be

provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study WN29922 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study WN29922.

4.5.12.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TIMING OF STUDY ASSESSMENTS

4.6.1 Screening and Pretreatment Assessments

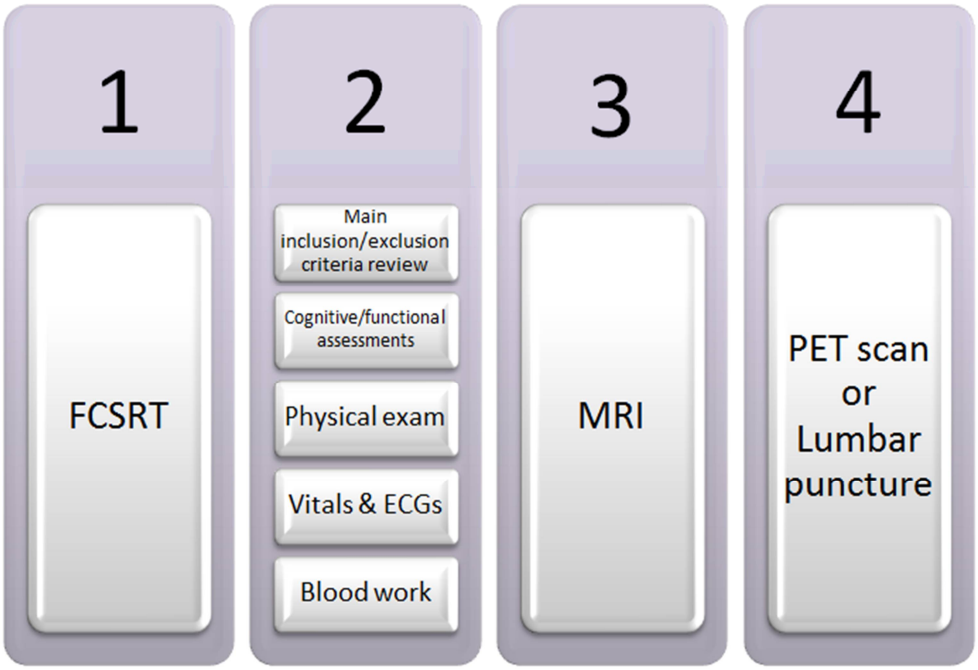
Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site. After providing written informed consent, patients who are willing to participate in the study will undergo all screening assessments within *12* weeks prior to the baseline visit, as detailed in the schedule of activities (see Appendix 1). Patients must fulfill all the entry criteria for participation in the study and the results must be available prior to the baseline visit.

The FCSRT *and MMSE assessments* may also be completed at prescreening. However, in this case, a separate prescreening consent would need to be signed and FCSRT *and MMSE* would not need to be repeated during the screening process. In case the patient would not qualify based on the FCSRT inclusion criteria, investigators have the option to repeat the FCSRT once after at least 6 months have elapsed if recruitment for the study is still ongoing.

In case of an abnormal laboratory or ECG result at screening that may normalize upon retest, investigators have the option to repeat the tests (prior to baseline and within the 8-week screening window) once to confirm the test results before randomizing a patient at baseline.

In rare cases in which a MRI scan needs to be repeated or any other unexpected delay due to logistical or technical reasons, the screening period may be extended by some days. Extending the screening period beyond *12* weeks must be approved by the Medical Monitor and should be for exceptional circumstances only; careful scheduling should remain a priority.

The recommended order of screening assessments is as follows:



ECG = electrocardiogram; FCSRT = Free and Cued Selective Reminding Test; MRI = magnetic resonance imaging; PET = positron emission tomography.

The recommended order of clinical assessments and rating scales at screening is shown below.

Patient Assessments	Study Partner Assessments
1. FCSRT (performed at prescreening or at screening) *10-min break (optional)* 2. *MMSE (performed at prescreening or at screening)* 3. *CDR (patient interview)*	CDR (study partner input)

CDR = Clinical Dementia Rating; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination.

CSF sampling, PET scan, and MRI scan at screening should be performed only once all other screening results are available and none exclude the patient from the trial.

If a patient does not qualify on the basis of applicable tests, the patient may be rescreened again after at least 3 months (6 months for FCSRT) have elapsed if recruitment for the study is still ongoing.

As noted in the exclusion criteria (see Section 4.1.2), patients may be rescreened after appropriate treatment if they were originally excluded for abnormal thyroid, folic acid, vitamin B-12, or HbA_{1c} results. Other laboratory tests that would exclude the patient may be repeated once (as an unscheduled laboratory assessment) if it is suspected that the abnormal result is transient and likely to be normal on repeat.

Patients may be rescreened if the protocol is amended such that they would satisfy the amended criteria and if recruitment for the study is still ongoing. In this case, all screening assessments must be repeated with the exception of lumbar puncture and prior PET scan if performed within the previous 12 months for this study and within eligible ranges. Given that *APOE* status will not change over time, there is no need to repeat clinical genotyping in case of rescreening.

Patients may be rescreened if there is a substantial change in the patient's condition (e.g., a disallowed medication was stopped) and if recruitment for the study is still ongoing and all eligibility criteria are met.

It is suggested that screening tests with the exception of the lumbar puncture, MRI scan, and PET scan be performed within 1 to 2 weeks of signing the Informed Consent Form (to allow adequate time for the remaining tests). As soon as all the results are available, and none exclude the patient from the trial, CSF collection and/or PET scan and MRI scan should be performed, if required.

It will take several days to receive the results of the MRI or CSF. On occasion the originally scheduled MRI or CSF collection day may need to be postponed and in the case of the MRI, it may need to be repeated. Therefore, the scheduling of these tests needs to be done carefully and should begin as soon as possible.

For patients enrolling on the basis of PET criteria, and for patients willing to participate in any of the PET substudies, scans can be obtained after all other screening results are available. For these patients, it is recommended that the MRI appointment should be scheduled to allow sufficient time for the PET scan to be performed and evaluated before the end of the screening period.

A positive PET scan using Amyvid™, Vizamyl™, or Neuraceq™ acquired outside this study may be permissible to confirm patient inclusion with Sponsor approval. Previously acquired PET scans must meet quality standards detailed in the PET Technical Operations Manual and must be centrally evaluated.

Roche may keep information about screening test results, medical history, and demographic information for all patients (including non-eligible patients) for future development of diagnostic tests related to Aβ, *APOE* genotype, and AD, as well as additional analyses.

4.6.2 Assessments at Baseline

In order to be randomized and to receive double-blind treatment, patients must have no significant change in medical, psychiatric, or neurological conditions or change in medication since screening. The recommended order of assessments and rating scales is as follows:

- Clinical assessments (e.g., CDR, MMSE, and ADAS-Cog), including all those that require study partner input, should be completed before any invasive safety assessments.
- Vital sign measurements, ECGs, blood draws for clinical laboratory assessments, PK, ADA, and plasma biomarker sampling, and urine samples are recommended to be conducted following scale assessments and must be performed prior to study drug administration.

The recommended order of clinical assessments/rating scales at baseline is as follows:

Patient Assessments	Study Partner Assessments
1. ADAS-Cog13	1. CDR (study partner input)
2. CDR (patient interview)	2. FAQ
10-min break (optional)	3. ADCS-ADL
3. MMSE	4. ZCI-AD
4. *Coding*	5. QoL-AD
5. Verbal Fluency Task	6. EQ-5D
10-min break (optional)	7. RUD-Lite
6. QoL-AD	8. NPI-Q
7. C-SSRS	

ADAS-Cog13 = Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living; CDR = Clinical Dementia Rating; C-SSRS = Columbia–Suicide Severity Rating Scale; EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; NPI-Q = Neuropsychiatric Inventory–Questionnaire; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

If assessments are split over 2 days, all safety assessments must be performed on the same day as the study drug administration.

4.6.3 Assessments during Treatment

Patients will receive up to 43 SC administrations of study drug over the course of 102 weeks. The final on-treatment efficacy and safety assessments are scheduled at Week 104, 2 weeks after the last dose.

The same recommended order of clinical assessments and rating scales as above for the baseline visit should be followed (omitting those that are not conducted per the schedule of activities; see Appendix 1).

Vital sign measurements, ECGs, blood draws for clinical laboratory assessments, PK, ADA, plasma biomarkers, and urine samples are recommended to be conducted following scale assessments and must be performed prior to study drug administration.

If assessments are split over 2 days, all safety assessments must be done on same day as the treatment administration.

On each dosing day, after all assessments prior to dosing have been completed (see the schedule of activities in Appendix 1), gantenerumab or matching placebo will be administered subcutaneously at room temperature. For the first four doses, patients should be observed for a minimum of 2 hours after dosing and then for a minimum of 1 hour after all remaining doses (i.e., Doses 5 and beyond). Patients should leave the study center after injections only if they appear to be tolerating the injections. When doses are to be administered remotely from the clinical sites, study drug administration may be performed only by qualified health care providers, as defined by local regulations, who must remain with the patients for a minimum of 1 hour after each injection and be equipped with rescue medications.

Rescue medications to treat anaphylactic and anaphylactoid reactions must be available at the site or at the dosing location for HN visits. Patients and their study partners will be alerted to watch for signs of anaphylactic and anaphylactoid reactions and to contact the study center as soon as possible if any such signs are noted.

Visits at which the patient receives study drug may take place within ± 7 days of the protocol-specified date for Q4W administration and ± 3 days of the protocol-specified date for Q2W administration per the schedule of activities in Appendix 1.

However, all visits should be scheduled as close as possible to the exact day. It is preferred that all assessments for a visit be performed on the same day, but if necessary, assessments may be performed over more than 1 day. Preferably, all clinical scales and assessments should be performed on the same day. Study drug administration should be performed only after all assessments and rating scales for the patient have been completed.

For sites and patients for whom this is practical, visits that require only dosing, vital sign measurements, urine pregnancy test, C-SSRS assessment, and adverse event assessment may be performed at an alternate location conducted by appropriate health care professionals.

Refer to Appendix 1 for the schedule of activities during the treatment period.

4.6.4 Procedures for New MRI Findings

In addition to any local reading according to local procedures and requirements, all MRI scans will be reviewed by an expert central reader within approximately 1 week of receipt and a report provided to the site. For the purposes of overall study relevant decisions and recommendations, including patient eligibility as well as for analysis, results from the expert central reader will be used. Any time the central reader identifies a new MRI finding the study center medical staff and the Sponsor will be rapidly notified (see Section 4.5.9).

Refer to Section *5.1.3* for instructions in the event of new MRI findings (ARIA-E and ARIA-H).

4.6.5 Assessments at Study Completion or Early Termination Visit

Patients who complete the double-blind treatment period (defined as completion of 102 weeks of study drug treatment) have to complete the final efficacy and safety assessment period 2 weeks following the last dose (Week 104), and subsequent 14-week and 50-week follow-up periods (Weeks 116 and 152, respectively).

All patients who withdraw from treatment or discontinue from the study early will be asked to return 2 weeks after the last dose of study drug in order to complete the early termination visit.

In addition patients who withdraw from treatment will be asked to return for collection of safety (except MRI) and limited efficacy data (i.e., the primary and secondary endpoints) at visits that have efficacy assessments (e.g., Week *52*) per the schedule of activities until the end of the study (including Weeks 104, 116, and 152).

Autopsy reports, including cause of death, for all patients who die during the study (i.e., prior to the Week 50 follow-up visit) should be requested.

Refer to the schedule of activities to be performed at the study completion (Week 104 or early termination visit) in Appendix 1.

4.6.6 Follow-Up Assessments

Patients who complete the double-blind treatment period (defined as completion of 102 weeks of study drug treatment) and who are not willing to enroll in the OLE will be asked to return to the clinic 14 weeks and 50 weeks after the last dose of study drug for follow-up visits (Weeks 116 and 152, respectively).

Patients who withdraw from treatment will be asked to return for collection of safety (except MRI) and limited efficacy data (i.e., the primary and secondary endpoints) at visits that have efficacy assessments (e.g., Week *52*) according to the schedule of activities until the end of the study (including Weeks 104, 116, and 152).

Patients who withdraw from study will only be asked to return 2 weeks after the last dose of study drug in order to complete the early termination visit.

When patients complete the treatment period or discontinue early, every effort should be made to ensure that the safety follow-up period and all related assessments are completed.

After the study completion or early termination visit, adverse events should be followed as outlined in Sections 5.5 and 5.6. Refer to the schedule of activities (see Appendix 1) for the list of assessments to be performed at the follow-up visits.

4.6.7 Unscheduled Assessments

Assessments at unscheduled visits should be determined by the investigator based on clinical relevance and appropriateness to the cause of the unscheduled visit. The schedule of activities in Appendix 1 allows for all assessments to be performed at unscheduled visits.

4.7 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Pregnancy
- Upon evidence of more than 15 ARIA-H, cumulatively
- Any disseminated leptomeningeal hemosiderosis

All patients who withdraw from treatment will be asked to return 2 weeks after last dose in order to complete the early termination visit *assessments*.

In addition, patients who withdraw from treatment will be asked to return for collection of safety (except MRI), and limited efficacy data (i.e., the primary and secondary endpoints) according to the schedule of activities until the end of the study (including Weeks 104, 116, and 152).

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

4.7.2 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Study termination or site closure
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance with the study and/or study procedures, defined as missing more than three consecutive dose administrations *(with Q4W dosing regimen) or more than six consecutive dose administrations (with Q2W dosing regimen)* because of non–safety-related reasons or more than *half of the dosing* visits in a calendar year

All patients who discontinue from the study early will be asked to return 2 weeks after last dose in order to complete the early termination visit.

Patient should be informed of circumstances under which their participation may be terminated by the investigator without the patient's consent. Any administrative or other reasons for withdrawal must be explained to the patient.

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn.

Patients who withdraw from the study will not be replaced.

4.7.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Futility analyses suggesting that treatment with gantenerumab is likely not effective.
- Sponsor determines it is the best interest of the patients.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.7.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Gantenerumab is not yet approved, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with gantenerumab in completed and ongoing studies. The identified risks for gantenerumab are outlined below. Please refer to the Gantenerumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for imaging-related abnormalities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Gantenerumab

5.1.1.1 Amyloid-Related Imaging Abnormalities

To date, clinical experience with gantenerumab reveals that ARIA events are dose-dependent and *APOE* ε4 dependent. These events are manageable with MRI monitoring and dose intervention algorithms. In addition, in case of clinical symptoms, the use of IV glucorticosteroids may be considered.

Rules for management of patients who develop ARIA-E or ARIA-H are provided in Appendix 6.

5.1.1.2 Injection-Site Reactions

Gantenerumab may cause a reaction when given as an SC injection. In studies with gantenerumab, the most common events occurring more frequently with gantenerumab than with placebo were local ISRs, such as reddening of the skin. The events were of mild intensity and resolved in most of the case without any treatment.

Detailed information on the characteristic signs and *symptoms* of *injection-site reactions* (e.g., erythema, pruritus) *will* be recorded on the *dedicated* eCRF *page.*

No gantenerumab-related immunogenicity reactions of major clinical relevance have emerged to date. Patients should be monitored for and alerted to the risk of any symptoms of hypersensitivity reactions.

5.1.2 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

5.1.3 Management of Patients Who Experience Selected Adverse Events

Patients will undergo brain MRI examinations prior to every dose increase (pre-uptitration MRI scans) and according to the schedule of activities once the target dose is achieved. The pre-uptitration MRI scans will determine eligibility for the next uptitration dose. Patients will be eligible for uptitration if there are no new ARIA-E, if the ARIA-E is resolved (BGTS=0), and if the criteria for discontinuation because of ARIA-H have not been met. In exceptional cases of ARIA-E that has significantly decreased and has being stable without associated clinical symptoms for several months as defined by the central reader, uptitration may be resumed.

In addition, the following dose adjustment and discontinuation rules for MRI findings will apply:

- In case of asymptomatic ARIA-E $\geq$1 and $<$4 BGTS: Continue study drug at the same dose level (i.e., do not uptitrate) and repeat MRI 4 weeks later.

  As long as BGTS is $<$4 and $\geq$1, continue study drug at the same dose level and continue MRI monitoring at 4-week intervals until the event resolves. When ARIA-E resolves, resume uptitration and MRI monitoring according the schedule of activities.

  If BGTS $\geq$4 or symptoms develop, refer to the rule below.

- In case of occurrence of symptoms in the presence of ARIA-E (any size) or asymptomatic ARIA-E with ≥4 BGTS: Temporarily interrupt study drug (but continue all assessments per schedule of activities) and implement MRI monitoring performed at 4-week intervals until symptoms and ARIA resolve.

  When symptoms and ARIA-E resolve, reintroduce study drug at the next scheduled dosing visit, at the same dose given at the time the event was detected and perform an MRI scan after the first dose for patients on Q4W regimen and after the second dose for patients on the Q2W regimen.

  If no new ARIA-E is detected, resume uptitration and obtain an MRI scan per the titration schedule. For patients on the Q2W regimen, perform another MRI scan 3 months after study drug reintroduction.
- Any recurrence of ARIA-E: Treat using the same procedures as for the first event (based on symptoms and BGTS).
- Patients who develop >15 ARIA-H cumulatively will be discontinued from study drug (the cumulative number should not include any disseminated leptomeningeal hemosiderosis, i.e., up to 3 focal leptomeningeal hemosiderosis; a focal leptomeningeal hemosiderosis is counted as an ARIA-H).
- In cases where both ARIA-E and ARIA-H occur, the most conservative approach should be followed.
- A PK sample will be obtained once the site becomes aware of the occurrence or worsening of ARIA-E or ARIA-H that meet the discontinuation criteria (e.g., an unscheduled visit).
- The investigators may choose to perform additional MRI monitoring for ARIA at any time.
- MRI monitoring of ARIA findings should be conducted at approximately 4-week intervals.

The iDMC will review the incidence of ARIA in an unblinded manner and may recommend adjustment of dosing regimen and/or ARIA management for the overall study population or for a specific *APOE* ε4 genotype.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.12)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe; the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.8)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.2.4 Selected Adverse Events

Data on associated symptoms and safety MRI scans will be collected for the following selected adverse events:

- ARIA-E: ARIAs suggestive of vasogenic edema and sulcal effusions
- ARIA-H: ARIAs suggestive of microhemorrhages and/or hemosiderin deposits

Please refer also to Section 5.3.5.1 for further details how to report ARIA events.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4). *The investigator is also responsible for reporting medical device complaints (see Section 5.4.4).*

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

In addition, after administration of a PET ligand, but prior to initiation of study drug, the following adverse events should be reported:

- *All adverse events (serious or non-serious) believed to be related to a PET ligand*
- *All serious adverse events occurring within 48 hours of PET ligand administration regardless of relatedness to the PET ligand*

For reporting of serious adverse events, see Section 5.4.2 for instructions. For non-serious PET ligand adverse events, a PET ligand specific non-serious adverse event reporting paper form should be completed and submitted to the Sponsor or its designee by scanning and emailing the form using the email address provided on the form.

After initiation of study drug, all adverse events will be reported until *the patient's last visit (including long-term follow-up visits).*

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

Table 3 provides guidance for assessing adverse event severity.

Table 3 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 ARIA Findings

Not every ARIA finding qualifies as an adverse event. An ARIA finding must be reported as an adverse event if it meets any of the following criteria:

- Is *symptomatic (i.e.,* accompanied by CNS symptoms*), and/or*
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)*, and/or*
- Is *otherwise* clinically significant in the investigator's judgment

Any accompanying symptoms should also be captured as separate adverse events.

It is the investigator's responsibility to review all ARIA findings.

Observations of the same clinically significant ARIA finding should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.2 Injection-Related Reactions

Individual signs and symptoms of injection-*site reactions (e.g., erythema, pain)* should be *reported on the Injection-Site Reaction eCRF. The overall diagnosis of injection-site reaction should be* captured on the Adverse Event eCRF. *Systemic reactions* should be recorded *as a single diagnosis.*

5.3.5.3 Diagnosis versus Signs and Symptoms

For adverse events, other than injection-related reactions (see Section 5.3.5.2), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.4 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.5 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes

more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.6 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5× ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.7 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.8 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.9 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of AD.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed to progression of AD, "Alzheimer's disease progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.10 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.11 Lack of Efficacy or Worsening of Alzheimer's Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is because of disease progression, it should be reported as an adverse event.

5.3.5.12 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization due to expected progression of underlying disease
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

5.3.5.13 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a study drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.14 Clinical Outcome Assessment Data

Adverse event reports will not be derived from clinical outcome assessment (COA) data by the Sponsor, and safety analyses will not be performed using COA data. *Sites are not expected to review the COA data for adverse events.*

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information

- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor: [redacted], *M.D. (Primary)*
Telephone No.:
Mobile Telephone No.:

Medical Monitor: [redacted]istic, M.D. *(Secondary)*
Telephone No.:
Mobile Telephone No.:

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.

In addition, the following serious adverse events should be reported after administration of a PET ligand and prior to initiation of study drug:

- *All serious adverse events believed to be related to the PET ligand*
- *All serious adverse events occurring within 48 hours of the PET ligand administration, regardless of relatedness to the PET ligand.*

The paper *Clinical Trial* Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until *the patient's last visit (including long-term follow-up visits)*. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 16 weeks after the last dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 *Reporting Requirements for Medical Device Complaints*

The investigator must report all medical device complaints (e.g., devices for study drug administration) to the Sponsor. The investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the pharmacy manual for further details). If the medical device results in an adverse event to the study patient, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously

communicate possible new safety findings to investigators, IRBs, Ecs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document: the Gantenerumab Investigator's Brochure.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The purpose of this study is to investigate the treatment effect of gantenerumab relative to placebo. The primary efficacy analysis will be based on an intent-to-treat (ITT) population, which will include all randomized patients during the global enrollment phase, with patients grouped according to their randomly assigned treatment.

Approximately *760* patients will be randomized in the global enrollment phase of this study. An increase in sample size may be considered in case of changes to sample size assumptions based on blinded data review or factors external to the study.

If at least 1 patient is enrolled *at sites* in *mainland* China*, Hong Kong, and Taiwan that are recognized by the CFDA* during the global enrollment phase, additional patients may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in the China.

The primary analyses of this study will include patients enrolled during the global enrollment phase; data from patients enrolled during the China extension will not be included in the primary analyses.

6.1 DETERMINATION OF SAMPLE SIZE

Determination of sample size is based on patients enrolled in the global enrollment phase. In this study, approximately *760* patients will be enrolled and randomized in 1:1 ratio to each treatment arm (gantenerumab or placebo) during the global enrollment phase. A sample size increase may be considered if factors external to the study or blinded study data analysis would warrant a change to the sample size assumption.

Additional patients may be randomized during the China extension if at least 1 patient is enrolled *at sites in mainland China, Hong Kong, and Taiwan that are recognized by the CFDA* during the global enrollment phase.

The estimated sample size required to demonstrate efficacy with regard to CDR-SOB is based on the following assumptions:

- The mean change in the CDR-SOB from baseline to Week 104 is *2.5* points in the placebo arm
- A common standard deviation across treatment arms for change of approximately *2.97* from baseline to Week 104 in the CDR-SOB
- Gantenerumab has a true effect of a 30% relative reduction in deterioration of CDR-SOB

Based on these assumptions*, and using a student's T-test with equal variance,* a sample size was calculated for 80% power to detect a true treatment effect of 30% relative reduction in deterioration of CDR-SOB at a two-sided α of 0.05.

Uncertainties on parameters affecting the power (e.g., dropout rate, study drug discontinuation rate, standard deviation, and placebo decline) were assumed to be equivalent to a drop-in sample size of up to around 35% and were corrected for accordingly. This calculation leads to a total of 760 patients in the study.

The sample size may be increased from *760* up to *1140* patients (*570* patients per arm). *The* decision whether to increase sample size will be based on a blinded assessment of pooled CDR-SOB change from baseline. Further details will be described in the Statistical Analysis Plan (SAP). The assessment will be performed by the Sponsor at a specified timepoint. *The sponsor will remain blinded.* The sample size will not be reduced on the basis of this assessment. Other factors external to the study may also trigger a decision to increase sample size.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, patient disposition, and incidence of protocol deviations will be summarized for the ITT population according to the randomly assigned treatment arms.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (such as age, sex, race, disease stage, *APOE* ε4 status, use and non-use of background therapy for AD) will be summarized descriptively for the ITT population, grouped according to the assigned treatment arm.

Descriptive summaries of continuous data will present the mean, standard deviation, median, and minimum and maximum. Descriptive summaries of discrete data will include frequencies expressed in terms of number and percentage of patients.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will use the ITT population, with patients grouped according to the treatment assigned at randomization.

6.4.1 Primary Efficacy Endpoint

The primary efficacy outcome measure is the change in CDR-SOB from baseline (Day 1) to Week 104. For the primary outcome measure, the difference in mean change from baseline to Week 104 between gantenerumab-treated patients and placebo-treated patients will be estimated. The analysis will use the ITT population, with patients grouped according to the treatment assigned at randomization. A mixed model repeated measures (MMRMs) analysis adjusting for baseline CDR-SOB score, disease stage, *APOE* ε4 status, geographic region and use of AD medication at baseline will be used to estimate the mean change from baseline to Week 104 for the primary endpoint.

The model will include the change from baseline in CDR-SOB as the dependent variable. The effects in the model will include baseline CDR-SOB score, disease stage, *APOE* ε4 status, geographic region, use of AD medication at baseline, treatment group, visit, and treatment-by-visit interaction. Visit week will be treated as the repeated variable within a patient. Disease stage, *APOE* ε4 status, geographic region, background medication at baseline, patient, treatment, and visit week will be treated as class variables. An unstructured variance-covariance structure will be applied to model the within-patient errors; in case of non-convergence, compound symmetry will be used.

The difference in the change from baseline of the patients randomized to gantenerumab from patients randomized to placebo will be estimated at each timepoint. The 95% CI and p-value for treatment difference will be presented.

All efforts will be made to minimize missing data. The Sponsor plans to request patients who discontinue early from study treatment to return for collection of safety and limited efficacy data (i.e., the primary and secondary efficacy endpoints) until Week 104. To explore the robustness of MMRM results for the primary efficacy conclusions sensitivity analyses (e.g., using multiple imputation and pattern mixture models) will be performed. Descriptive summaries of the number of patients with missing data, the timing, and reasons for discontinuation from the study will also be provided by treatment group.

Additional details will be documented in the SAP.

6.4.2 Secondary Efficacy Endpoints

The absolute change from baseline in the continuous secondary efficacy endpoints listed in Section 2, Table 2 (including cognition/function endpoints, global endpoints, disease pathology biomarkers, and endpoints measuring other AD symptoms and effects) will be analyzed using an MMRM analysis model similar to that described above for the primary efficacy endpoint.

For time-to-event endpoints, the Kaplan-Meier method will be used to estimate the median time-to-event for each treatment arm. The Cox proportional hazard model stratified by the randomization stratification factors will be used to estimate the hazard ratio and its 95% CI. The two-sided log-rank test, stratified by the randomization

stratification factors, will be used to perform hypothesis testing for assessing treatment difference between the two treatment arms at a 5% significance level.

In order to protect the overall type I error rate for the study when incorporating the hypothesis testing of the primary endpoint *and secondary endpoints* into the analysis, the fixed sequence testing procedure (Westfall and Krishen 2001) will be used to adjust for multiple comparisons. The first *endpoint that* will be tested *is*:

- Change from baseline to Week 104 in CDR-SOB

The order of testing for other secondary endpoints will be defined in the SAP.

The treatment difference in the primary endpoint (the change from baseline to Week 104 in the CDR-SOB) will be tested at a two-sided 5% overall significance level. The overall significance level will be maintained using the O'Brien-Fleming boundary. If this test result is statistically significant at either the interim or the final analysis, the secondary endpoints will be tested for significance in the predefined order *as specified in the SAP*. If any test result is not statistically significant, testing of the subsequent endpoints will not occur.

6.4.3 Exploratory Efficacy Analyses

Subgroup analysis of efficacy results will be performed for subgroups defined by age, sex, race, stage of disease (prodromal AD vs. mild AD), *APOE* ε4 status, geographic region, use and non-use of background therapies for AD, and other clinically relevant factors at baseline.

6.4.4 Pharmacodynamic and Exploratory Biomarker Analyses

PD and exploratory biomarker endpoints will be analyzed using descriptive statistics, subgroup analysis, or statistical models if appropriate. For longitudinally measured endpoints, the change from baseline and the difference between patients randomized to gantenerumab and patients randomized to placebo will be estimated if appropriate. Exploratory biomarkers may be reported separately.

6.5 SAFETY ANALYSES

The safety-analysis population will include all randomized patients who receive at least one dose of study drug, with patients grouped according to the treatment actually received, as defined in the SAP.

- Incidence, nature, and severity of MRI safety findings: ARIA-E and ARIA-H
- Incidence, nature, and severity of serious adverse events
- Incidence, nature, and severity of adverse events
- Incidence of adverse events of special interest
- Incidence of treatment discontinuations due to adverse events

- Mean changes in clinical laboratory tests from baseline over time; incidence of treatment-emergent abnormal laboratory values and abnormal laboratory values reported as adverse events
- Mean change in ECG assessments from baseline over time and incidence of abnormal ECG assessments
- Physical and neurologic examination abnormalities
- Mean change in vital signs (blood pressure, pulse rate) from baseline over time and incidence of abnormal vital sign measurements
- Changes in CSSR-S scores from baseline over time
- Number and proportion of ADA-positive and ADA-negative patients during both the treatment and follow-up periods will be summarized by treatment group

6.6 PHARMACOKINETIC ANALYSES

Plasma concentration data for gantenerumab will be tabulated and summarized. Descriptive summary statistics will include the arithmetic mean, median, range, SD, and coefficient of variation, as appropriate. Because a sparse PK sampling design is being used, population (non-linear mixed-effects) modeling will be used to analyze the dose concentration–time data of gantenerumab. Information from other clinical studies may be incorporated to establish the PK model. The selection of parameters and the derivation of individual measures of exposure, such as AUC, C_{max}, and trough serum concentration, will depend on the final PK model used for this analysis. The results of this modeling analysis may be reported separately from the clinical study report.

CSF concentrations of gantenerumab will be tabulated and summarized as appropriate from the substudy.

The influence of background medication on the pharmacokinetics of gantenerumab will be explored and, if appropriate, concentration–effect relationships may be assessed post hoc for PD, efficacy, or safety measures.

Additional PK analyses will be conducted as appropriate and may be reported separately from the clinical study report.

6.7 INTERIM ANALYSIS

6.7.1 Planned Interim Analysis

An interim analysis for efficacy and futility is to be conducted approximately 24 months after 50% of the targeted study enrollment has been reached.

An independent data coordinating center will be responsible for the interim analyses and study results will only be reviewed by the iDMC. The Sponsor will remain blinded.

The iDMC may recommend stop for futility if the failure criterion is met. The failure criterion will represent a low probability of a positive study outcome given the data observed at the time of interim analysis. The failure criterion will be prespecified in the iDMC SAP.

In contrast, the iDMC may "declare the study positive for overwhelming efficacy" if the study meets the success criterion on the primary endpoint. The success criterion is defined as the p-value threshold determined by standard Lan and DeMets methodology (1983) for group sequential design using the O'Brien-Fleming boundary function. If the study continues beyond the interim analysis, the critical value at the final analysis will be adjusted accordingly.

6.7.2 Optional Interim Analysis

Based on availability of information pertaining to gantenerumab or other compounds with similar mode of action that may emerge during the course of this study, the Sponsor may choose to conduct an additional interim analysis for futility and/or efficacy beyond the interim analysis mentioned above.

An independent data coordinating center will be responsible for the interim analyses and study results will only be reviewed by the iDMC. The Sponsor will remain blinded.

Details of the interim analyses, including the decision to conduct the optional interim analysis, the rationale, timing, and statistical details for the analyses (such as the data that would be reviewed by the iDMC and futility or efficacy thresholds) will be documented in a SAP, and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.

6.8 CHINA EXTENSION ANALYSIS

The objective of the China extension and the China subpopulation analyses is to assess the treatment effects of gantenerumab in a population of patients *enrolled at sites in mainland China, Hong Kong, and* Taiwan *that are recognized by the CFDA and* to investigate the consistency in treatment effect between the China subpopulation and the global population for the purpose of registration in China.

All patients enrolled in the global enrollment phase in China will be included in the primary analysis. The analysis of the China extension will be conducted after the end of China extension and will be reported separately from the primary analysis and at a subsequent point in time.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of

eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. All electronic data from external vendors will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

COA data will be collected through the use of an electronic device (tablet) provided by a vendor. Some COA data may be audio recorded for quality assurance purposes. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR, Part 11). The electronic data are available for view access only via secure access to an online Web portal. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC CLINICAL OUTCOME DATA

Patients, study partners, and appropriate site staff will use an electronic device (tablet) to capture COA. For some COA, audio recordings may be used for quality assurance purposes. All data will be transmitted via Web automatically after entry into a centralized database maintained by the electronic device vendor.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and

machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic COA data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or *Home* Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the

local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and

data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

The overall procedures for quality assurance of clinical study data are described in the Roche standard operating procedures. This study will be sponsored by F. Hoffmann-La Roche Ltd. Roche will provide clinical operations oversight, site monitoring and management, data management support, and medical monitoring.

Study drug distribution may occur through an IxRS (see Section 4.2). Central facilities may be used for study assessments (i.e., ECG, lumbar puncture, specified laboratory tests, PK, rating scales, and MRI and PET imaging, as applicable).

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

Table 1: Schedule of Activities (Week –*12* to Week 32; Dose Escalation with Q4W Administration)

Assessment/Procedure	*Prescreen* & Screening	Baseline	Dose Escalation Period									Unsched Visit
	Weeks *–12* to –1	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	
Dose Number		1 [a]		2	3	4	5 [b]	6 [b]	7 [a]	8 [b]	9 [b]	
Dose level in milligrams (mg)		*120*		*120*	*120*	*255*	*255*	*255*	*510*	*510*	*510*	
Informed consent(s) [c]	x											
Review of inclusion and exclusion criteria	x	B										
Medical history, personal status, and demographics	x											
Weight *and height* [t]	x											x
Clinical genotyping samples	x											
Clinical RNA samples	x											
Urinalysis [d]	x											
Urine sample for drugs of abuse [e]	x											
Coagulation (PT)	x											
Viral serology (HIV, hepatitis B, and hepatitis C)	x											
FCSRT	*P* [f]											
12-Lead electrocardiogram [g]	x	B				B			B			x
PK plasma sample [h]		B	x						B			x
ADA sample		B							B			x
Serum chemistry [i] and hematology [j]	x	B							B			x

Appendix 1
Schedule of Activities (cont.)

Table 1: Schedule of Activities (Week –*12* to Week 32; Dose Escalation with Q4W Administration) (cont.)

Assessment/Procedure	*Prescreen &* Screening	Baseline	Dose Escalation Period									Unsched Visit
	Weeks –*12* to –1	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	
Dose number		1[a]		2	3	4	5[b]	6[b]	7[a]	8[b]	9[b]	
Dose level in milligrams (mg)		*120*		*120*	*120*	*255*	*255*	*255*	*510*	*510*	*510*	
Plasma biomarker sample	x								B			x
Complete physical examination (includes neurological systems)[k]	x											x
Limited physical examination[l]									B			x
MRI scan[m, n]	x[o]					B			B			x
CSF *and matching serum* sampling[m, p] or PET scan[m, p]	x											
CDR	P&SP	P&SP							P&SP			P&SP
ADAS-Cog13		P							P			P
Verbal Fluency Task		P							P			P
Coding		*P*							*P*			*P*
ADCS-ADL		SP							SP			SP
FAQ		SP							SP			SP
MMSE	P*f*	P							P			P
EQ-5D		SP							SP			SP
QoL-AD		P&SP							P&SP			P&SP
ZCI-AD		SP							SP			SP
RUD-Lite		SP							SP			SP
NPI-Q		SP							SP			SP

Appendix 1
Schedule of Activities (cont.)

Table 1: Schedule of Activities (Week –*12* to Week 32; Dose Escalation with Q4W Administration) (cont.)

Assessment/Procedure	*Prescreen* & Screening	Baseline	Dose Escalation Period									Unsched Visit
	Weeks *–12* to –1	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	
Dose number		1 [a]		2	3	4	5 [b]	6 [b]	7 [a]	8 [b]	9 [b]	
Dose level in milligrams (mg)		*120*		*120*	*120*	*255*	*255*	*255*	*510*	*510*	*510*	
C-SSRS BL/SLV		P							P			P
Vital signs [q]	x	B	B	B	B	B	B	B	B	B	B	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [r]	x	B		B	B	B	B	B	B	B	B	x
Study drug administration [h, s]		x		x	x	x	x	x	x	x	x	

ADAS-Cog13=Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL=Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR=Clinical Dementia Rating; CSF=cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D=EuroQol-Five Dimensions; FAQ=Functional Activities Questionnaire; FCSRT=Free and Cued Selective Reminding Test; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; NPI-Q=Neuropsychiatric Inventory–Questionnaire; PET=positron emission tomography; PK=pharmacokinetic; Prescreen=prescreening; Q4W=every 4 weeks; QoL-AD=Quality of Life–Alzheimer's Disease; RBR=Research Biosample Repository; RUD-Lite=Resource Utilization in Dementia–Lite; SC=subcutaneous; Unsched=unscheduled; Wk=week; ZCI-AD=Zarit Caregiver Interview–Alzheimer's Disease.

B=before study drug administration; P=patient completion; P&SP=patient and study partner completion; SP=study partner completion.

Notes: The visit window is ±7 days for dosing days. Patients should return to initial planned schedule per randomization for subsequent visits.

In case of rescreening a patient, all screening assessments must be repeated other than the lumbar puncture and amyloid PET testing if performed within the previous 12 months for this study and are within the eligible ranges. In addition, clinical genotyping will not need to be repeated in case of rescreening.

[a] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first, and within 1 week prior to the first dose at baseline. All safety assessments (e.g., vital signs, blood tests, and ECGs) should be completed on the day of dosing.

[b] Visit suitable for home administration of gantenerumab.

Appendix 1
Schedule of Activities (cont.)

Table 1: Schedule of Activities (Week –*12* to Week 32; Dose Escalation with Q4W Administration) (cont.)

[c] Patients participating in the optional prescreening period must provide written consent before any study-specific prescreening assessments are performed. If patient is eligible and decides to participate in the screening assessments, he or she will need to provide new written consent.

[d] Performed at the site by dipstick for blood, protein, glucose, and pH.

[e] Urine samples will be analyzed for the presence of the following drugs: amphetamine, benzodiazepines, cannabinoids, opiates, cocaine, barbiturates, and methadone.

[f] *Can be done at prescreening or at screening. There is no need to repeat the test at screening if* performed at prescreening.

[g] Electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 5 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws, brain MRI scans, and lumbar puncture). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

[h] Accurate recording of the date and time of study drug administration and PK sampling is critical.

[i] Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). During the screening period (Week –1 to Week –8), hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[j] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelets, basophils, eosinophils, lymphocytes, monocytes, neutrophils, and WBC–other total counts.

[k] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

[l] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in patient notes.

[m] CSF *and matching serum* sampling, and PET and MRI scans at screening should be performed once all other screening results are available and none exclude the patient from the study.

[n] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[o] Includes resting-state functional MRI and DTI outcome measures where available.

[p] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters. For post-baseline visits, lumbar puncture *as well as serum sampling* should be performed prior to dosing. Only one method (CSF or PET) confirming amyloid is necessary for all patients.

Appendix 1
Schedule of Activities (cont.)

Table 1: Schedule of Activities (Week –*12* to Week 32; Dose Escalation with Q4W Administration) (cont.)

[q] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the patient is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined by radial pulse and will be recorded as beats per minute. Pulse rate should be counted for a minimum of 20 seconds at each assessment.

[r] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[s] Study drug administration should be performed only after all assessments/rating scales for the patient are completed (unless indicated otherwise). Study drug will be administered to patients by SC injection. Patients should be observed up to 2 hours after dosing. After the fourth injection visit, the observation time may be reduced to 1 hour. Study personnel *preparing and* administering study drug must not be involved with any efficacy assessments or safety evaluations.

[t] *Height measured at screening only.*

Appendix 1
Schedule of Activities (cont.)

Table 2: Schedule of Activities (Week 36 to the End of Study: *510* mg Q2W)

Assessment/Procedure	Treatment Period										Final Efficacy and Safety Assessments	Follow-Up Period for Patients Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
	Wk 36	Wk 38	Wk 40	Wk 41	Wk 42–50	Wk 52	Wk 54–74	Wk 76	Wk 78–102	Wk 103	Wk 104 [a, b]	Wk 116	Wk 152		
Dose number	10	11	12		13–17 [c]	18 [a]	19–29 [c]	30 [a]	31–43 [c]						
Dose level in milligrams (mg)	*510*	*510*	*510*		*510*	*510*	*510*	*510*	*510*						
12-Lead ECG						B		B			x	x		x	x
PK plasma sample [d]				x (Site visit)		B		B		x (Site visit)		x	x	x	x
ADA sample						B		B				x	x	x	x
Clinical RNA sample											x				
Serum chemistry [e] and hematology [f]						B		B			x	x	x	x	x
Plasma biomarker sample						B					x			x	x
Complete physical examination (including neurological systems) [g]											x			x	x
Limited physical examination [h]						B		B							x
Weight											x			x	x
MRI scan [i]	B				Wk 48 [j]		Wk 60	B			x [j]			x [j]	x
CSF [k] *and matching serum* sampling (for patients enrolled based on CSF eligibility criteria only)						x					x			x [k]	
CDR						P&SP		P&SP			P&SP		P&SP	P&SP	P&SP

Appendix 1
Schedule of Activities (cont.)

Table 2: Schedule of Activities (Week 36 to the End of Study: *510* mg Q2W) (cont.)

Assessment/Procedure	Treatment Period										Final Efficacy and Safety Assessments	Follow-Up Period for Patients Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
	Wk 36	Wk 38	Wk 40	Wk 41	Wk 42–50	Wk 52	Wk 54–74	Wk 76	Wk 78–102	Wk 103	Wk 104 [a, b]	Wk 116	Wk 152		
Dose number	10	11	12		13–17 [c]	18 [a]	19–29 [c]	30 [a]	31–43 [c]						
Dose level in milligrams (mg)	*510*	*510*	*510*		*510*	*510*	*510*	*510*	*510*						
ADAS-Cog13						P		P			P		P	P	P
Verbal Fluency Task						P		P			P		P	P	P
Coding						*P*		*P*			*P*		*P*	*P*	*P*
ADCS-ADL						SP		SP			SP		SP	SP	SP
FAQ						SP		SP			SP		SP	SP	SP
MMSE						P		P			P		P	P	P
EQ-5D						SP		SP			SP			SP	SP
QOL-AD						P&SP		P&SP			P&SP			P&SP	P&SP
ZCI-AD						SP		SP			SP			SP	SP
RUD-Lite						SP		SP			SP			SP	SP
NPI-Q						SP		SP			SP			SP	SP
C-SSRS BL/SLV						P		P			P			P	P
Vital signs [l]	B	B	*B*		B	B	B	B	B		x	x	x	x	x
Concomitant medications	x	x	*x*	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	*x*	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Activities (cont.)

Table 2: Schedule of Activities (Week 36 to the End of Study: *510* mg Q2W) (cont.)

Assessment/Procedure	Treatment Period										Final Efficacy and Safety Assessments	Follow-Up Period for Patients Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
	Wk 36	Wk 38	Wk 40	Wk 41	Wk 42–50	Wk 52	Wk 54–74	Wk 76	Wk 78–102	Wk 103	Wk 104 [a, b]	Wk 116	Wk 152		
Dose number	10	11	12		13–17 [c]	18 [a]	19–29 [c]	30 [a]	31–43 [c]						
Dose level in milligrams (mg)	*510*	*510*	*510*		*510*	*510*	*510*	*510*	*510*						
Urine pregnancy test [m]	B	B	*B*		B	B	B	B	B		x	x		x	x
Study drug administration [d, n]	x	x	*x*		x	x	x	x	x						

ADAS-Cog13=Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL=Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR=Clinical Dementia Rating; CSF=cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D=EuroQol-Five Dimensions; FAQ=Functional Activities Questionnaire; FCSRT=Free and Cued Selective Reminding Test; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; NPI-Q=Neuropsychiatric Inventory–Questionnaire; OLE=open-label extension; PET=positron emission tomography; PK=pharmacokinetic; Q2W=every 2 weeks; QoL-AD=Quality of Life–Alzheimer's Disease; RBR=Research Biosample Repository; RUD-Lite=Resource Utilization in Dementia–Lite; SC=subcutaneous; Unsched=unscheduled; Wk=week; ZCI-AD=Zarit Caregiver Interview–Alzheimer's Disease.

B=before study drug administration; P=patient completion; P&SP=patient and study partner completion; SP=study partner.

Notes: The visit window is ±3 days for dosing days. Patients should return to initial planned schedule per randomization for subsequent visits.

[a] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vitals, blood tests, and ECGs) should be completed on the day of dosing.

[b] Transition to OLE study for patients who are eligible to participate.

[c] Visit suitable for home administration of gantenerumab.

[d] Accurate recording of the date and time of study drug administration and PK sampling is critical.

Appendix 1
Schedule of Activities (cont.)

Table 2: Schedule of Activities (Week 36 to the End of Study: *510* mg Q2W) (cont.)

[e] Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). At Week 52 and Week 104, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[f] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

[g] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

[h] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in patient notes.

[i] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[j] Includes resting-state functional MRI and DTI outcome measures, where available.

[k] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For patients enrolling based on CSF eligibility criteria, CSF *and matching serum* samples are mandatory at Week 104 and optional at Week 52; the need of CSF collection at early termination visit will be discussed on a case-by-case basis with the Medical Monitor.

[l] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the patient is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined by radial pulse and will be recorded as beats per minute. The pulse rate should be counted for a minimum of 20 seconds at each assessment.

[m] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[n] Study drug administration should be performed only after all assessments and rating scales for the patient are completed (unless indicated otherwise). Study drug will be administered to patients by subcutaneous injection (full details are provided in the pharmacy manual). Patients should be observed for up to 2 hours after dosing. After the fourth injection visit, this observation time may be reduced to 1 hour. Study personnel *preparing and* administering study drug must not be involved with any efficacy assessments or safety evaluations.

Appendix 2
National Institute on Aging/Alzheimer's Association Criteria for Mild Alzheimer's Disease

NIA/AA Category	Description
Probable dementia: core clinical criteria Meets criteria for dementia described earlier in the text, and, in addition, has the following characteristics:	A. Insidious onset: Symptoms have a gradual onset over months to years, not sudden over hours or days B. Clear-cut history of worsening of cognition by report or observation; and C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories: 1. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text. 2. Non-amnestic presentations • Language presentation: The most prominent deficits are in word finding, but deficits in other cognitive domains should be present. • Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present. • Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present. D. The diagnosis of probable AD dementia should not be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or non-fluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

AD = Alzheimer's disease; *APOE* = apolipoprotein E; CSF = cerebral spinal fluid; NIA/AA = National Institute on Aging/Alzheimer's Association; PET = positron emission tomography.

Appendix 2
National Institute on Aging/Alzheimer's Association Criteria for Mild Alzheimer's Disease (cont.)

NIA/AA Category	Description
Probable AD dementia with increased level of certainty	**Probable AD dementia with documented decline** In persons who meet the core clinical criteria for probable AD dementia, documented cognitive decline increases the certainty that the condition represents an active, evolving pathologic process, but it does not specifically increase the certainty that the process is that of AD pathophysiology. Probable AD dementia with documented decline is defined as follows: evidence of progressive cognitive decline on subsequent evaluations based on information from informants and cognitive testing in the context of either formal neuropsychological evaluation or standardized mental status examinations. **Probable AD dementia in a carrier of a causative AD genetic mutation** In persons who meet the core clinical criteria for probable AD dementia, evidence of a causative genetic mutation (in APP, PSEN1, or PSEN2) increases the certainty that the condition is caused by AD pathology. The working group noted that carriage of the ε4 allele of the *APOE* gene was not sufficiently specific to be considered in this category.
Probable AD dementia with evidence of the AD pathophysiological process	AD dementia is part of a continuum of clinical and biological phenomena. AD dementia is fundamentally a clinical diagnosis. To make a diagnosis of AD dementia with biomarker support, the core clinical diagnosis of AD dementia must first be satisfied. Relevant biomarkers include amyloid-β (CSF or PET) and tau (CSF or PET).

AD = Alzheimer's disease; *APOE* = apolipoprotein E; CSF = cerebral spinal fluid; NIA/AA = National Institute on Aging/Alzheimer's Association; PET = positron emission tomography.

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Appendix 3
National Institute on Aging/Alzheimer's Association Criteria for Prodromal Alzheimer's Disease (Mild Cognitive Impairment due to Alzheimer's Disease)

NIA/AA Category	Clinical and Cognitive Criteria
Clinical criteria	• Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time) • Objective evidence of impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains) • Preservation of independence in functional abilities • Not demented
Etiology of MCI consistent with AD pathophysiological process	• Rule out vascular, traumatic, medical causes of cognitive decline, when possible • Provide evidence of longitudinal decline in cognition, when feasible • Report history consistent with AD genetic factors, when relevant
Prodromal AD dementia with evidence of the AD pathophysiological process	Prodromal AD is part of a continuum of clinical and biological phenomena. Prodromal AD is fundamentally a clinical diagnosis. To make a diagnosis of prodromal AD with biomarker support, the core clinical diagnosis of prodromal AD must first be satisfied. Relevant biomarkers include amyloid-β (CSF or PET) and tau (CSF or PET).

AD = Alzheimer's disease; CSF = cerebral spinal fluid; MCI = mild cognitive impairment; NIA/AA = National Institute on Aging/Alzheimer's Association; PET = positron emission tomography.

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Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data

The population pharmacokinetic positron emission tomography (PK-PET) response analysis of the gantenerumab Phase III study WN25203 data and aducanumab Phase Ib PET study model was built using pooled information from the gantenerumab Phase III study WN25203 and the aducanumab Phase Ib PRIME study. Details about how this population analysis was conducted and evaluated are provided herein.

1. MATERIALS AND METHODS

1.1 MODELING HYPOTHESIS

Based on the high degree of similarity between gantenerumab and aducanumab, it was assumed that both compounds share the same PK properties in terms of disposition, metabolism, elimination, and the same relationship between in serum concentrations and reduction in standardized uptake value ratio (SUVr) amyloid PET.

It was also assumed that the SUVr data from aducanumab and gantenerumab could be pooled given that they were derived using the same whole cerebellum reference region and that the sensorimotor region used only in the composite SUVr of aducanumab was having little effect on the SUVr values.

1.2 PHARMACOKINETIC AND PHARMCODYNAMIC DATA

A PK-pharmacodynamic (PD) dataset for PET model was built using information from the Phase III gantenerumab study (WN25203) together with information from Phase Ib aducanumab trial (PRIME).

2.2.1 Gantenerumab PK and PET Data

2.2.1.1 PK Information

Each patient participating in Study WN25203 provided samples for measurement of their PK serum concentrations at the following scheduled timepoints: Weeks 1, 8, 20, 44, 53, 68, 100, and 101.

The PK data from Study WN25203 were analyzed using a population PK model that was previously developed on the basis of Phase I studies.

The Phase I PK database comprised data from 235 patients and healthy volunteers for a total of 4082 PK observations. It contained data from both IV and SC administration, single and multiple repeated doses administered every 4 weeks (Q4W), with dose values ranging for the repeated dose administrations from 6 mg to 200 mg for the IV, 105 and 225 mg for the SC, and up to 300 mg SC and 400 mg IV when administered once. A two-compartment model with a 0 order followed

by first-order absorption best described the Phase I data. Population parameter values are reported in Table 1.

Table 1 Population PK Parameters Estimated from Phase I Study Data

Parameter	Mean	RSE%	BSV%	RSE%
CL (L/day)	0.336	3.20%	26.1%	6.9%
V2 (L)	3.52	5.60%	31.3%	18.5%
Q (L/day)	0.869	9.50%	55.5%	10.6%
V3 (L)	6.38	4.10%	24.9%	10%
KA (/day)	0.22	8.90%	52.2%	21.1%
D1 (/day)	0.0821	7.10%	96.6%	8.9%
F1 (–)	0.494	3.90%	42.8%	10.5%
PROP.ERR	0.196	5.40%		
ADD.ERR (μg/mL)	0.0121	21.70%		

ADD_ERR = additional error; CL=clearance; D1 = zero order rate constant; F1 = absolute bioavailability; KA = absorption rate constant; KeO = rate constant for drug transfer from serum to effect compartment; PK = pharmacokinetic; POW = power; PROP_ERR = proportional error; Q = intercompartmental clearance; RSE = relative standard error; SLOP = slope; V2 = central compartment; V3 = peripheral volume 3.

The population PK model was used to perform an empirical Bayesian analysis in non-linear mixed-effects model (NONMEM) of the PK data collected from Study WN25203 and to derive for each patient the individual PK parameters, as well as an estimation of the individual average concentrations over the period of observation.

2.2.1.2 PET Information

Among the 799 patients enrolled in Study WN25203, 114 patients participated in the amyloid PET substudy (using the AV-45 ligand). Scans were performed at baseline, Weeks 20, 60, and 100. For patients entering the 2-year, double-blinded portion of the trial (Part 2), another scan was obtained at Week 156.

PET data up to Week 100 (inclusive) were considered for the PK-PD modeling investigations, and the PET database comprised a total of 348 SUVr observations determined using the whole cerebellum as the reference region.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

2.2.2 Aducanumab PK and PET PD Data

Aducanumab PK and PET data were extracted from a poster (n°ADPD5–2113) and from slides that were presented at the 12th International Congress on Alzheimer's Disease and Parkinson's Disease (ADPD) in March 2015 in Nice, France.

The aducanumab data were collected in the Phase Ib, randomized, double-blind, placebo-controlled study (PRIME) in patients with prodromal or mild Alzheimer's disease. The study design involved a parallel-group design, with a 54-week treatment period. Patients received 14 IV infusions of aducanumab Q4W; four dose groups were evaluated, including the placebo group, and included the 1-mg/kg, 3-mg/kg, 6-mg/kg, and 10-mg/kg dose groups, respectively. SUVr measurements were performed at baseline, Week 26, and Week 54 and were determined using the whole cerebellum as the reference region.

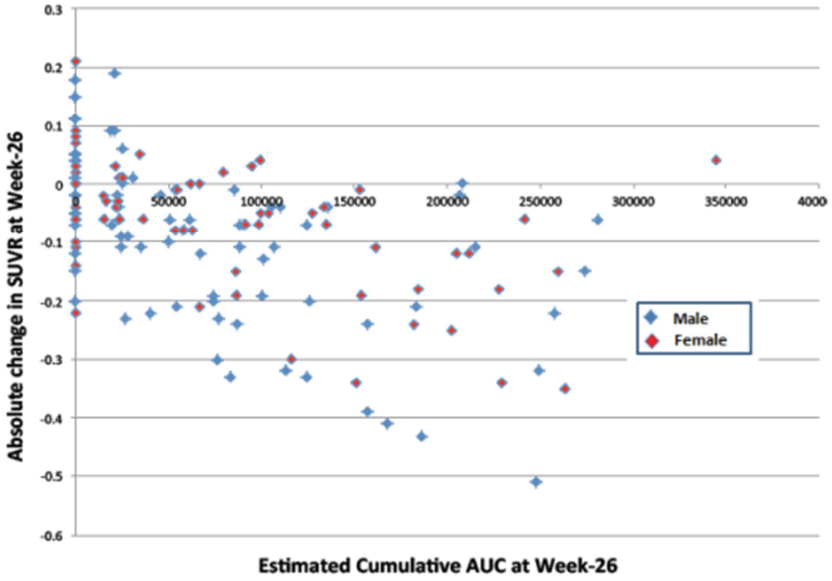
The following figures were used from the aducanumab poster and slides:

- A figure displaying the individual absolute change in SUVr at Week 26 in function of the individual cumulative area under the concentration-time curve (AUC) at Week 26 (see Figure 1)
- A table presenting the time course of the mean SUVr up to Week 54 by dose group (see Table 2)
- A figure displaying the relationship between the individual cumulative AUC at Week 26 and the four doses investigated in the PRIME study (see Figure 2)

The individual data, as depicted in Figure 1, were extracted and a database of 123 patients with their respective cumulative AUC values at Week 26 and the absolute change from baseline in SUVr. The mean data from Figure 2 were used to extrapolate the individual aducanumab PET data at Weeks 26 to 54 and, also, to assign a mean SUVr baseline value to each aducanumab dose group. In addition, the data from Figure 2 were used to determine from which dose group the individual cumulative AUC values at Week 26 from Figure 1 were most likely derived.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

Figure 1 Individual Absolute Change in SUVr Observed in Aducanumab Data at Week 26 with Respect to Cumulative Exposure



AUC = area under the concentration–time curve; SUVr = standardized uptake value ratio.
Source: Hang et al. 2015.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

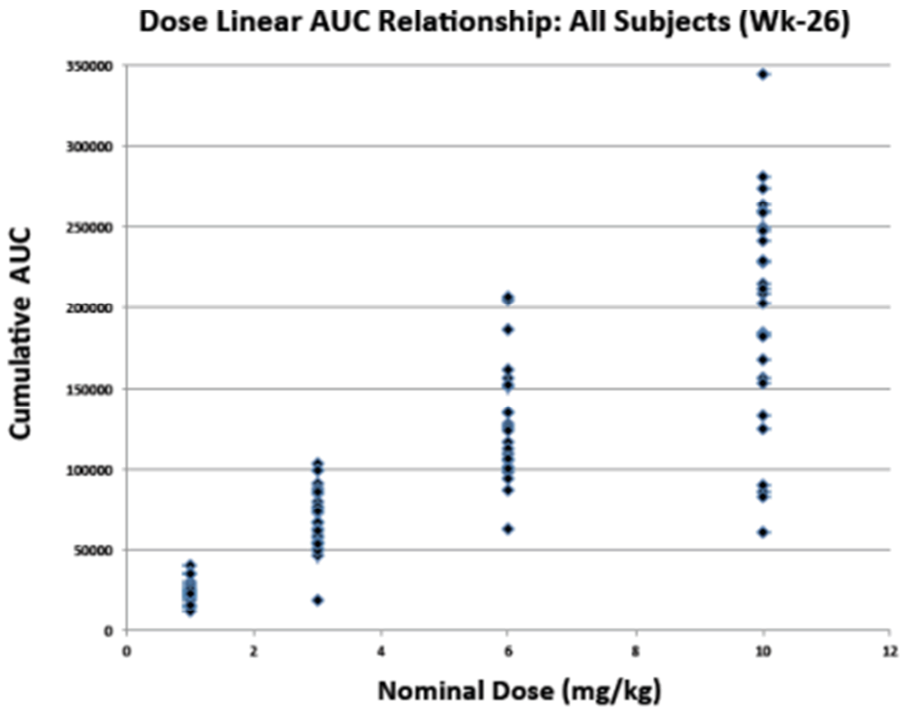
Table 2 Mean Composite PET SUVr Data Observed in the Aducanumab Phase Ib Trial (PRIME) per Dose Group, Using the Whole Cerebellum as Reference Region

	Observed Mean Composite SUVr		
Dose Group	Baseline	Week 26	Week 54
Placebo	1.45	1.42	1.42
1 mg/kg	1.45	1.395	1.346
3 mg/kg	1.471	1.365	1.3
6 mg/kg	1.44	1.288	–
10 mg/kg	1.434	1.223	1.152

SUVr = standardized uptake value ratio.

Source: Data derived from presented slide at ADPD conference.

Figure 2 Individual Dose–Exposure Relationship Observed in the Aducanumab Phase Ib Trial (PRIME)



AUC = area under the concentration–time curve.

Note: Subjects demonstrating low cumulative aducumab exposures were primarily due to missed doses.

Source: Hang et al. 2015.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

2.3 POPULATION PK-PD METHODS

2.3.1 Structural PK-PD Model

Several structural PK-PD models were evaluated to best describe the link between exposure and SUVr PET. The tested models included a direct relationship, as well as an indirect relationship, using an effect-compartment model to take into account a time delay for the concentrations in serum to reach the effect site.

Furthermore, several types of drug effect were tested, including a linear model, a power model, an E_{max} model, and a sigmoid E_{max} model.

No placebo models were evaluated because no specific placebo response was noticed during the observations period.

An additive error model was used for the residual variability. The baseline PET SUVr values were used as covariate in the model, but with an associated residual error of the same magnitude of the additive error model.

Inter-individual variability was tested on the PK-PD parameters by assuming a log-normal distribution.

2.3.2 PK-PD Model Selection and Evaluation

Models were selected by means of visual inspection of basic goodness-of-fits plots, including, but not limited to, plots of the observed data versus population (PRED) and individual predictions (IPRED), plots of individual weighted residuals (IWRES) versus IPRED, and the distribution of weighted residuals (WRES) over time. Relative standard errors (RSE) of the parameters were also compared to measure parameter precision. The NONMEM objective function value (OFV) was used to discriminate between nested models. This discrimination was based on a significance level of 0.05, which corresponds to a decrease of >3.84 in OFV (for one degree of freedom), as the difference in OFV is approximately χ^2 distributed.

Additionally, visual predictive check (VPC) was performed to test the model appropriateness by means of computing confidence intervals (CIs) derived from 1000 simulated data sets, using the final model and final parameter estimates, for each statistic (i.e., the median, the 5th and the 95th percentiles). Several VPCs were performed, either to test the appropriateness of the model when predicting the gantenerumab and aducanumab pooled dataset or to focus separately on the two compounds datasets. Furthermore, they were produced per level of exposure as well as per level of doses.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

2.3.3 Computer Programs

The analyses were performed in NONMEM Version 7.2, using FOCE INTERACTION (Beal and Sheiner 1992). Graphics and NONMEM datasets were created using Version 3.1.2 and/or the SAS system for Windows, Version 9.3.

2.4 COVARIATE ANALYSIS

Only limited covariate information was available from the aducanumab data, and an exploratory graphical analysis of individual post-hoc parameters was conducted only for the following covariates: PET baseline values, compound type, sex, and dose.

3. RESULTS

3.1 DATA

The final PK-PD dataset combining aducanumab and gantenerumab data included 237 patients with a total of 693 PET SUVr observations.

3.2 POPULATION EXPOSURE SUVr PET MODEL

The relationship between exposure and the PET SUVr reduction time course was best described by using a power model combined with an effect compartment to account for the delay between exposure and PET response. The model equations are as follows:

$$\mathrm{PET(time)} = \mathrm{Base} * \left(1 - \mathrm{SLOP} * (\mathrm{Conc_E(time)})^{\mathrm{POW}}\right)$$

with $$\frac{\mathrm{dConc_E(time)}}{\mathrm{dtime}} = \mathrm{Ke0} * (\mathrm{Conc(time)} - \mathrm{Conc_E(time)})$$

with Base the individual PET SUVr baseline value, $\mathrm{Conc_E}$ the predicted concentration at effect site, Conc the predicted concentration in serum, $\mathrm{Ke0}$ the rate constant for drug transfer from serum to effect compartment, and SLOP and POW the parameters driving the drug effect.

Parameter values are reported in Table 3.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

Table 3 Estimated Population PK-PD Parameters

Parameter	Mean (RSE%)	Value Inter-Individual Variability (RSE%)
Ke0 (Day $^{-1}$)	1.74×10^{-3} (38%)	127.3% (14%)
Equilibration half-life (weeks)	57	
SLOP	0.019 (33%)	—
POW (–)	0.716 (11%)	—
ADD_ERR	0.0659 (5%)	

ADD_ERR = additional error; KeO = rate constant for drug transfer from serum to the effect compartment; PD = pharmacodynamic; PK = pharmacokinetic; POW = power; RSE = relative standard error; SLOP = slope.

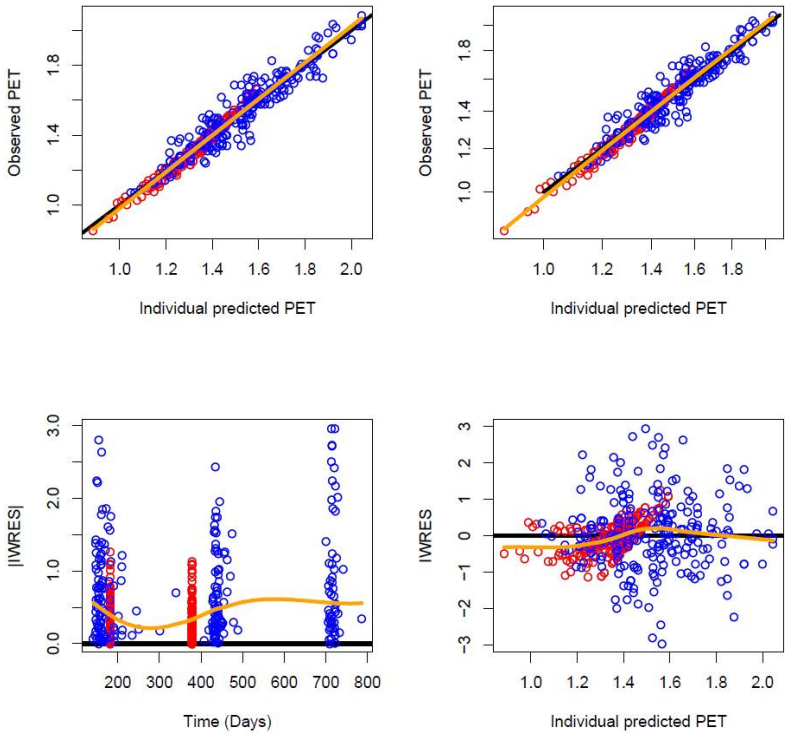
Inspection of the goodness-of-fit plots reported in Figure 3 shows that the final PK-PD model describes the data adequately without obvious bias in the population or individual predicted PET values. The VPCs are shown in Figures 5–7. The shaded areas indicate the 90% CIs (i.e., 5th and 95th percentiles) computed from simulations. The median and the 5th and 95th percentiles of the observed PK profiles are contained in their respective CIs, indicating that the final PK-PD model captures both the central tendency and the between-subject variability of both gantenerumab and aducanumab pharmacodynamics in the target populations of patients with prodromal and mild Alzheimer's disease.

3.3 COVARIATE ANALYSIS

The exploratory graphical covariate analysis is reported on Figure 4. Although a small trend between PET baseline values and estimated individual Ke0, this graphical analysis did not reveal any relevant covariate relationships that would require further investigation.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

Figure 3 Goodness-of-Fit Plots for the Final PK-PD Model

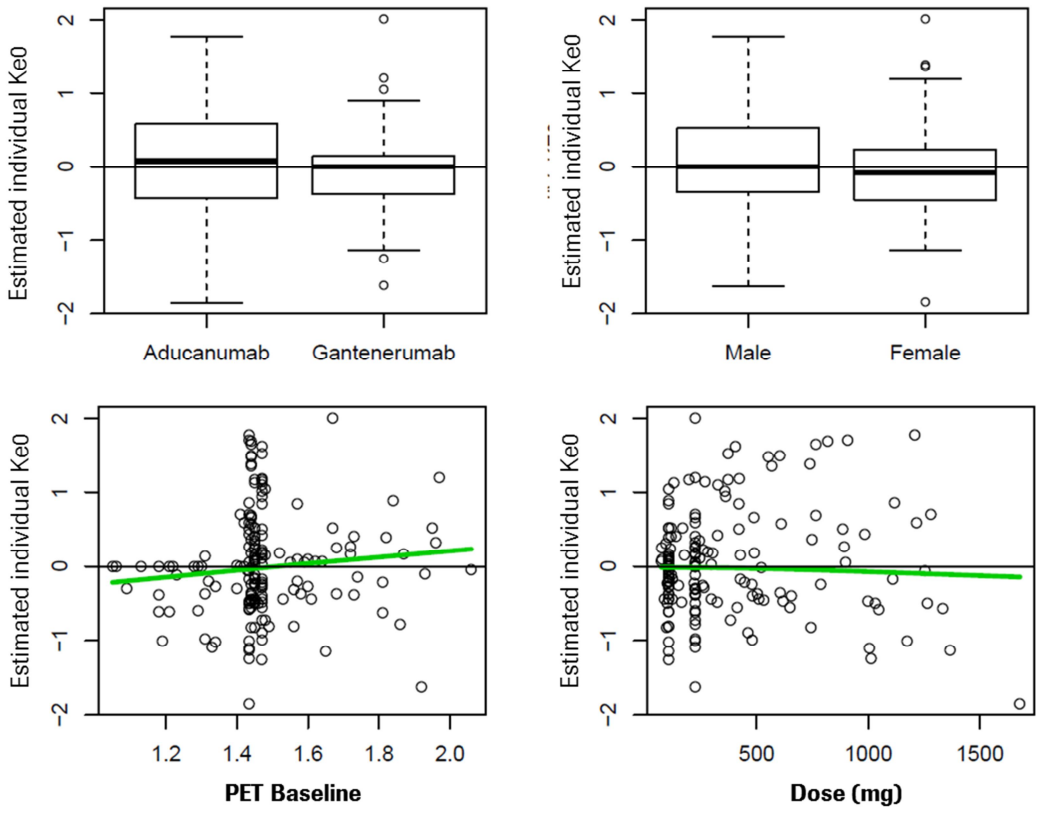


IWES = individual weighted residual value; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

Note: The red dots represent the aducanumab compound, and blue dots represent gantenerumab compound. The orange lines correspond to a smoothing of the data.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

Figure 4 Exploratory Analysis of Covariates (by Compound Type, Sex, PET Baseline Value, and Dose [in milligrams] Value with Respect to Estimated Individual Ke0)

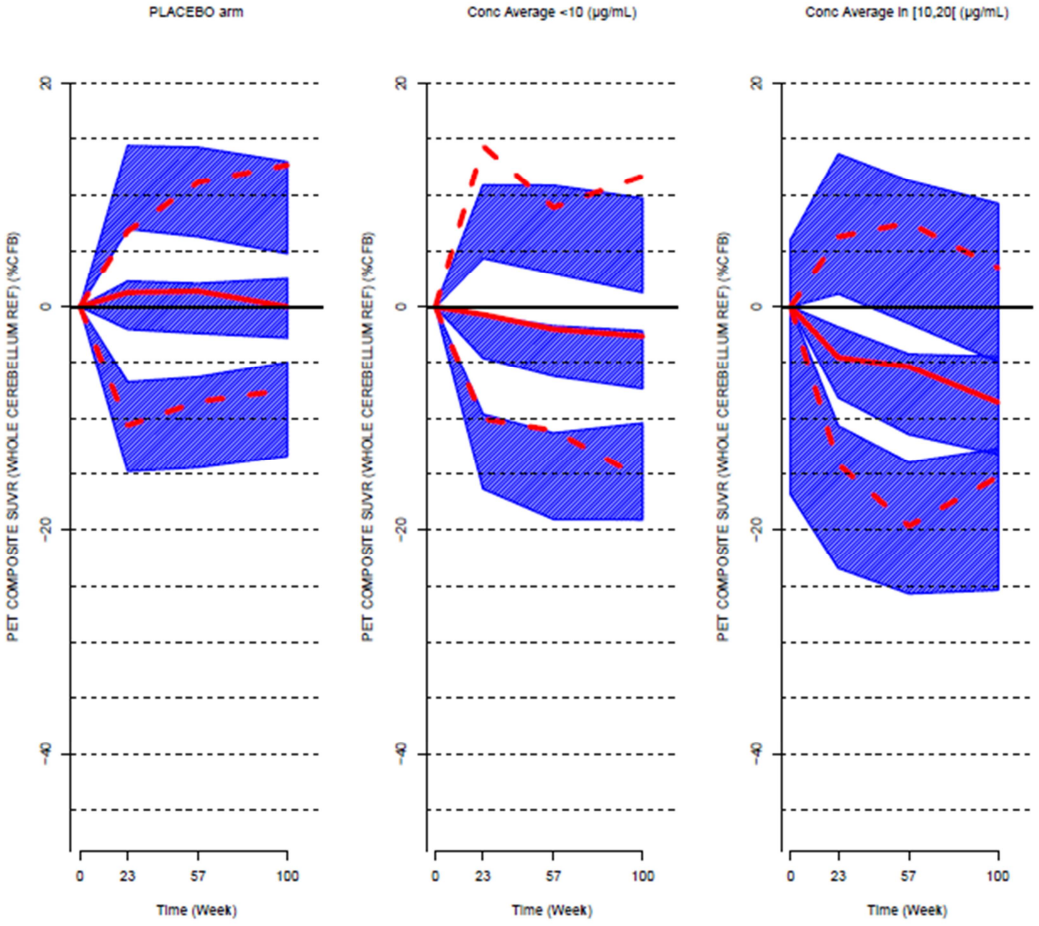


KeO = rate constant for drug transfer from serum to the effect compartment; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

Note: Dose was investigated in milligrams, using a mean weight of 70 kg for doses the aducanumab PRIME study. The green line corresponds to a smoothing of the data.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

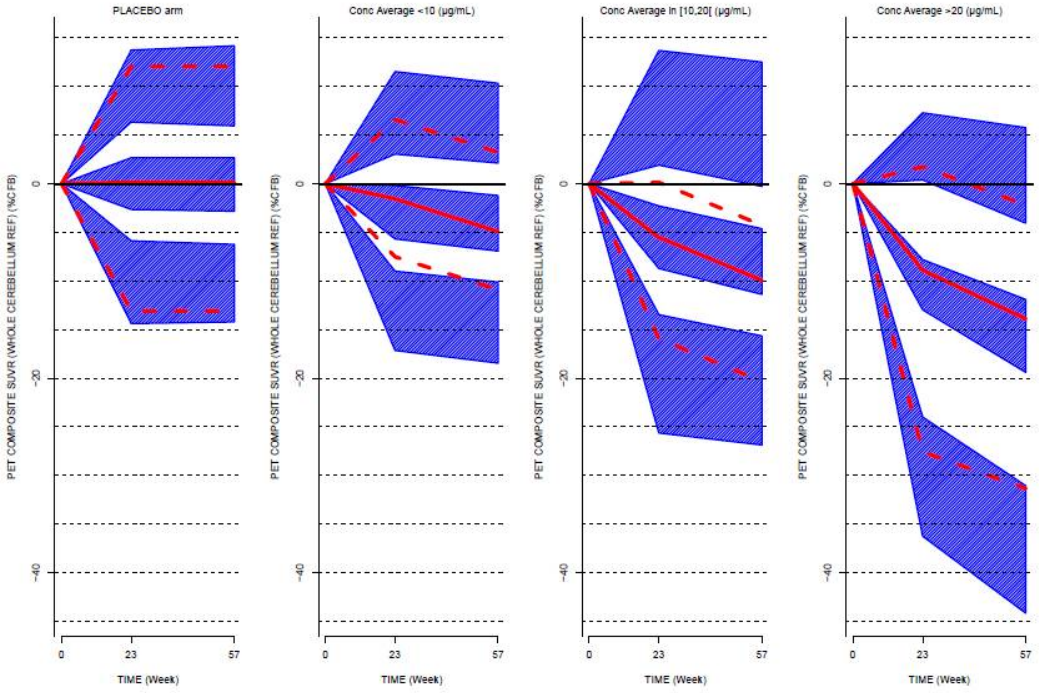
Figure 5 Visual Predictive Check of the PET Model by Category of Serum Concentration Exposure for the Gantenerumab WN25203 Alone



CFB = change from baseline; Conc = concentration; KeO = rate constant for drug transfer from serum to the effect compartment; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

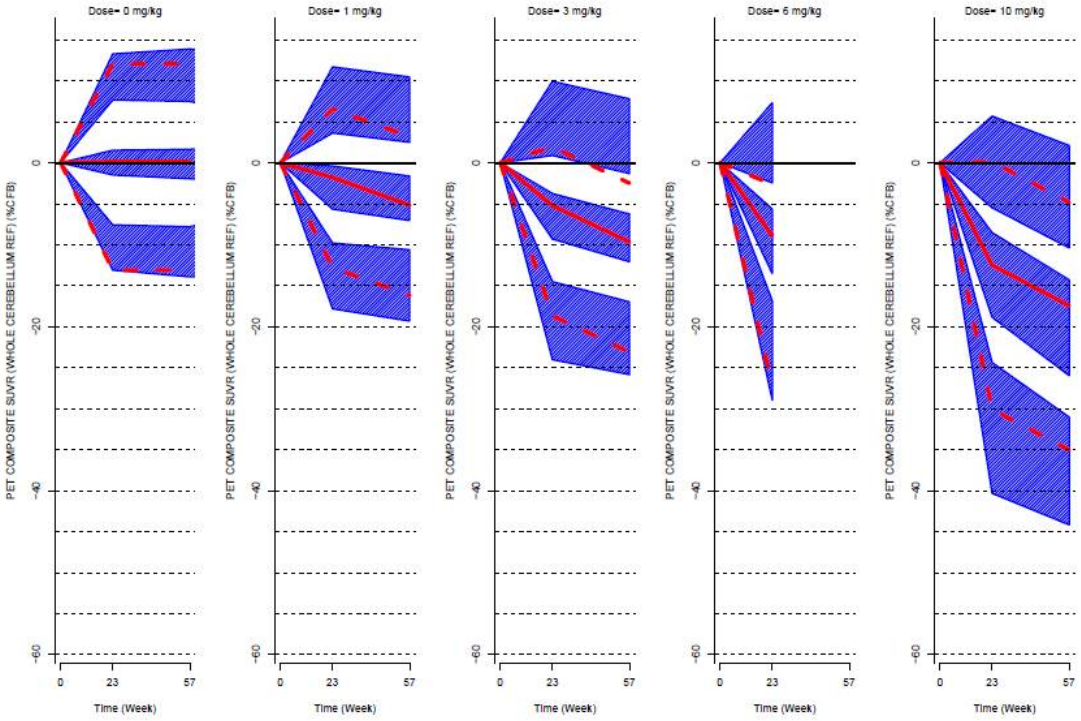
Figure 6 Visual Predictive Check of the PET Model Per Category of Serum Concentration Exposure for the Aducanumab PRIME Study Alone



KeO = rate constant for drug transfer from serum to the effect compartment; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

Figure 7 Visual Predictive Check of the PET Model by Category of Expected Dose Group for the Aducanumab PRIME Trial Alone



KeO = rate constant for drug transfer from serum to the effect compartment; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

REFERENCES

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Hang Y, Chiao P, Sevigny J, et al. Pharmacokinetic and pharmacodynamic (PK-PD) assessment and covariate analysis of aducanumab (BIIB037) in a randomized, double-blind, placebo-controlled, Phase 1b study (PRIME) in subjects with prodromal or mild Alzheimer's disease. 12th International Congress on Alzheimer's and Parkinson's Disease. Poster presentation. March 2015. Nice, France.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model

1. BACKGROUND

Hutmacher et al. (2013) presented a pharmacodynamic (PD) model for bapineuzumab addressing the first occurrence of amyloid-related imaging abnormalities, or ARIAs, of "vasogenic edema" (ARIA-E) events. Patients received constant dose regimens of 0.5, 1, and 2 mg/kg given every 13 weeks over 1.5 years. A total of 2435 patients with 243 ARIA-E events were analyzed. As shown below, a log hazard model was developed that included three elements:

- A baseline value (I_{BS}) reflecting a constant ARIA-E hazard for apolipoprotein E allele ε4 (*APOE* ε4) gene carriers and non-carriers, respectively
- Plasma drug concentrations (c) of bapineuzumab modulating the ARIA-E hazard through the maximum effect (E_{max}) of drug and 50% of the effective concentration (EC_{50}) parameters
- A time component continuously suppressing the ARIA-E hazard by the time (t) since first dosing. ET_{50} and γ modulated this effect.

$$\log h(t) = I_{BS} + \frac{E_{\max} \cdot c(t)}{c(t) + EC_{50}} \cdot \frac{ET_{50}^{\gamma}}{ET_{50}^{\gamma} + t^{\gamma}}$$

Because no model parameters were reported in Hutmacher et al. 2013, the parameters were derived from predicted time-concentration and time-hazard curves presented in Hutmacher et al. 2013 after digitizing the respective graphs for 0.5 mg/kg in *APOE ε4* carriers. I_{BS} parameters were obtained from the graphs directly, whereas the other parameters were calculated from the digitized data using MATLAB (or matrix laboratory) and maximum likelihood estimation. Parameter values are shown in Table 1.

Table 1 Estimated Pharmacodynamic Parameters for Bapineuzumab

I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (μg/mL)
8.7E-6 (non-carrier) 3.55E-5 (carrier)	323.441	2.146	6.891	2.64

2. ARIA EVENTS UNDER CONSTANT DOSING REGIMENS

The above model was applied to the double-blind phase of Study WN25203, in which patients received constant dose regimens of 105 and 225 mg of gantenerumab. Owing to paucity of ARIA event data and the assumed independence between time and study drug–related hazard model parameters, I_{BS}, ET_{50}, and γ were fixed to the bapineuzumab values, and only E_{max} and EC_{50} were estimated.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

The concentration-time course for gantenerumab in Study WN25203 was derived from a population pharmacokinetic (PK) model previously developed for Phase I studies. It covers both intravenous (IV) and subcutaneous (SC) administration, as well as single and multiple repeated doses every 4 weeks, with a range of dose values for the repeated dose administrations from 6 mg to 200 mg for IV administration, 105 mg and 225 mg for SC administration, and up to 300 mg SC and 400 mg for IV administration when given only once. The parameters for this model are presented in Table 2.

Table 2 Pharmacokinetic Parameters for Gantenerumab

CL (L/day)	Q (L/day)	V_2 (L)	V_3 (L)	k_a (1/d)	F1 (1/d)	D (1/d)
0.336	0.869	3.152	6.38	0.22	0.494	0.0821

An update of the population PK model parameters was not considered as newly available drug concentrations were within prediction ranges from the established PK model. The maximum likelihood estimation of the log hazard model parameters E_{max} and EC_{50} was performed using NONMEM software. ARIA-E events were interval censored with a cutoff at 742 days. A total of 797 patients with 50 ARIA-E events were analyzed.

Parameter estimates are shown in Table 3.

Table 3 ARIA-E Parameters for Gantenerumab

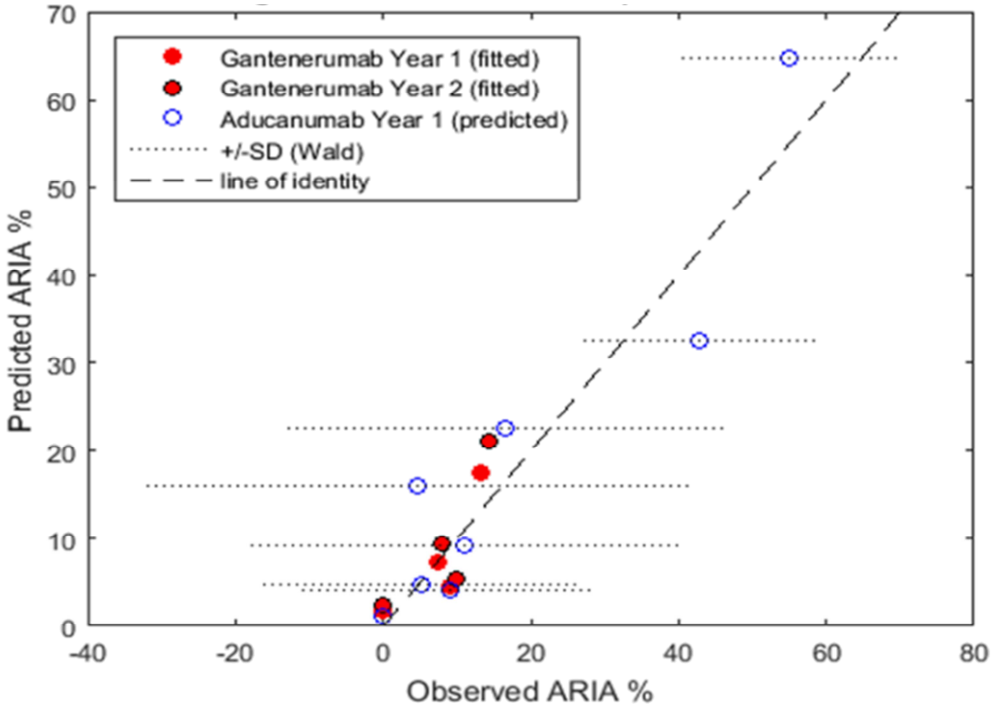
I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (μg/mL)
8.7E-6 (non-carrier) F 3.55E-5 (carrier) F	323.44 F	2.15 F	6.05±2.33	8.60±7.13

amyloid-related imaging abnormality–edema/effusion; F = fixed.

On inspection of the aducanumab PRIME study data (Sevigny et al. 2015), it became clear that the PK properties of gantenerumab and aducanumab are very similar. This supported an opportunity to test the hazard $PK\text{-}PD$ model applied to gantenerumab on IV aducanumab ARIA-E data. The ARIA–E model, which already provides a good description of the gantenerumab ARIA-E data in Study WN25203 after 1 and 2 years of treatment, respectively, also predicted the aducanumab Phase Ib ARIA-E data with a great degree of accuracy (see Figure 1), including the ARIA rate differences across *APOE* ε4 allele groups (see Figure 2), even though this approach is limited based on external aggregated data. This finding indicated that doses much larger than those

given in Study WN25203 can be described by the hazard model, provided that a constant dose regimen is used.

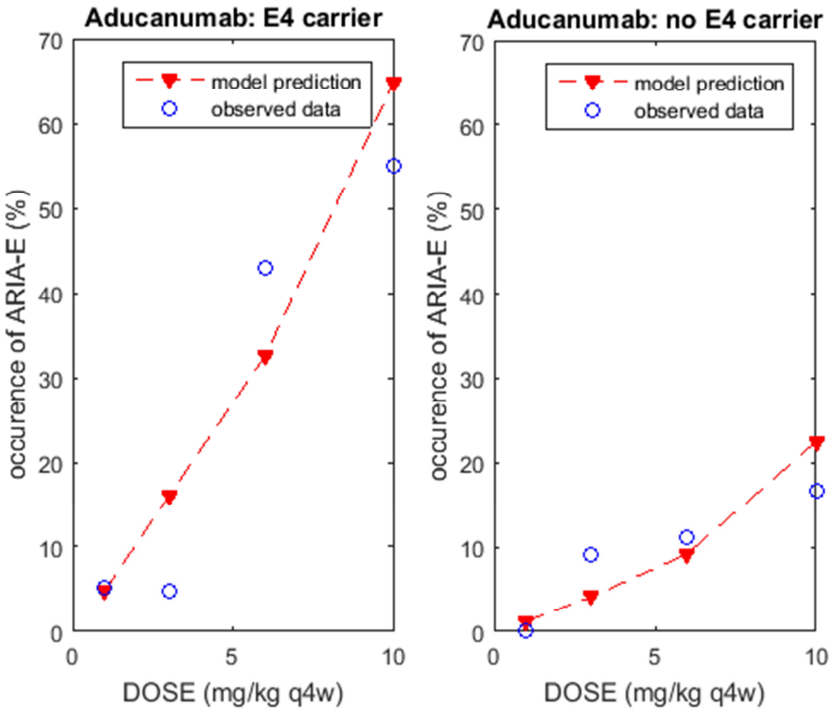
Figure 1 ARIA-E Prediction for IV Aducanumab Using Bapineuzumab Hazard Model Adapted to SC Gantenerumab



ARIA = amyloid-related imaging abnormality; ARIA-E = amyloid-related imaging abnormality–edema/effusion; IV = intravenous; SC = subcutaneous; SD = standard deviation.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Figure 2 Model-Based Predictions of ARIA-E Occurrence for Aducanumab by *APOE ε4* Carrier and Non-Carrier Status and Dose for a Q4W Dosing Regimen: Comparison to Observed Data in the PRIME Study



APOE ε4= apolipoprotein E, allele ε4; ARIA = amyloid-related imaging abnormality; ARIA-E = amyloid-related imaging abnormality–edema/effusion; IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous.

3. ARIA EVENTS UNDER DOSE TITRATION REGIMENS

3.1 MODELING DATABASE AS OF 6 DECEMBER 2016

To check the validity of the model under titration conditions, two patient groups were selected from the open-label extension studies of WN25203 and WN28745. The first group comprised 71 patients who received increasing doses of gantenerumab and received placebo during the double-blind phase of the study. The second group comprised 417 patients who received a constant dose of gantenerumab and who did not have treatment-free intervals of more than 70 days. The first group is representative for the intended Phase III design, and the second group was included to enhance the database and link the model to previously established results (see Table 4).

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Table 4 Patient Population Included in ARIA-E Model Building (Database as of 6 December 2016)

Number of Patients (Number of Events)	Study WN25203	Study WN28745	Total	Comment
Total included in study	**797 (63)**	**371 (35)**	**1168 (108)**	
Placebo treatment	236 (2)	111 (3)	347 (5)	Excluded from model building
Total included in study on active drug	**561 (61)**	**260 (32)**	**821 (103)**	
Total on active drug before OLE, or treatment gaps >70 days	125 (11)	108 (23)	333 (44)	Excluded from model building
Total included in model building	**436 (50)**	**52 (9)**	**488 (59)**	
Titrated without prior treatment	19 (1)	52 (9)	71 (10)	Included in model building
Constant dosing, and treatment gaps <70 days	417 (49)	—	417 (49)	Included in model building

ARIA-E = amyloid-related imaging abnormality–edema/effusion; OLE = open-label extension.

As noted previously, the maximum likelihood estimation was performed using NONMEM software. Estimated model parameters were E_{max} , EC_{50} and the baseline risk for carriers and non-carriers. ARIA-E events were observation interval censored.

Parameter estimates are shown in Table 5.

Table 5 ARIA-E Parameters for Gantenerumab When Applied to Titration Data

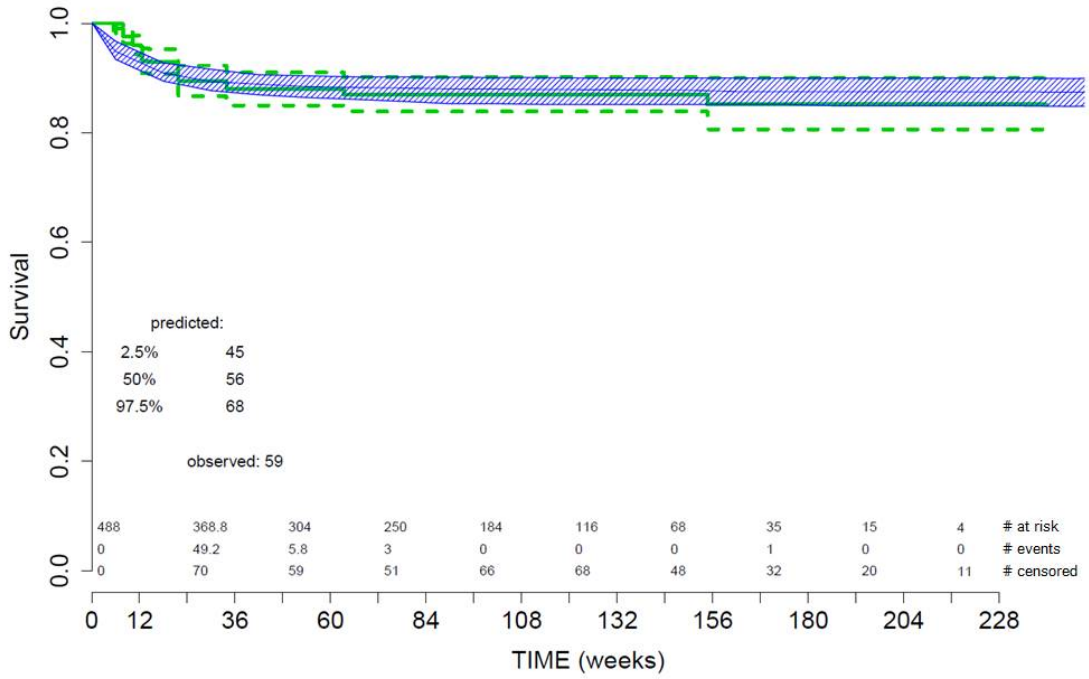
I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (μg/mL)
5.84 ± 4.22 E-6 (non-carrier) 11.9 ± 7.30 E-6 (carrier)	323.44 F	2.15 F	7.12 ± 1.03	5.16 ± 2.85

ARIA-E = amyloid-related imaging abnormality–edema/effusion; F = fixed.

Visual predictive checks were performed to assess model performance. As shown in Figure 3, the overall model performance was acceptable. Figure 4 presents a condition that was excluded from the model building. The apparent bias in the prediction might be attributable to a SCarlet RoAD study effect, which will be followed up during ongoing completion of the database.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Figure 3 Visual Predictive Check on Database Used for Model Building

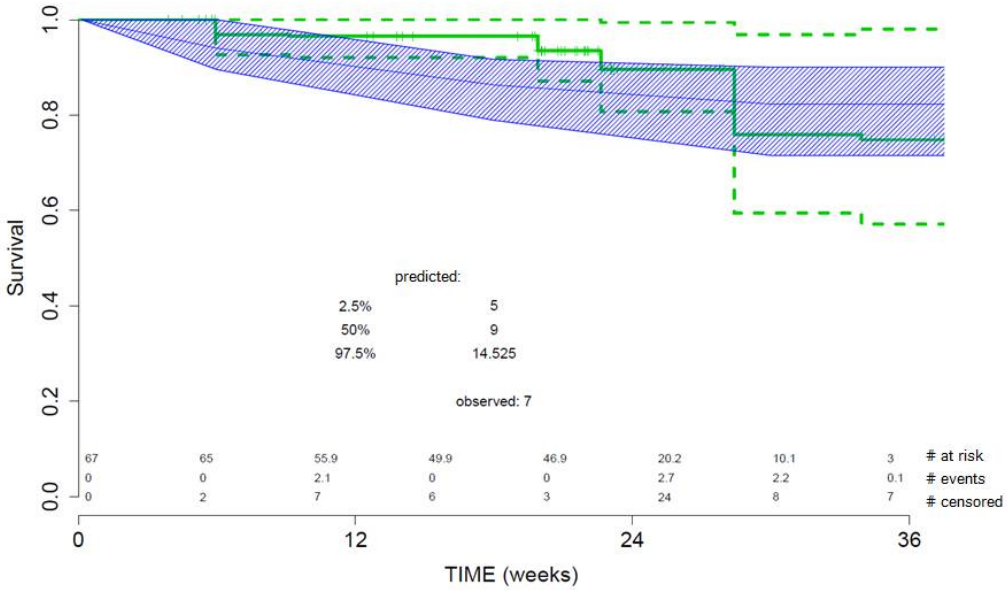


ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% [median], and 97.5%) and the actual observed number of events.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Figure 4 Visual Predictive Checks: Patients in SCarlet RoAD Study with Treatment Interruption >70 Days from Time 0 at Start of Open-Label Extension WN25203



ARIA-E = amyloid-related imaging abnormality–edema/effusion; OLE = open-label extension.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% [median], and 97.5%) and the actual observed number of events.

3.2 MODELING DATABASE AS OF 3 MARCH 2017

Table 6 presents an updated ARIA-E model building using data based on the cutoff date of 3 March 2017. In Table 7, ARIA-E parameters for gantenerumab are summarized when applied to titration data.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Table 6 Patient Population Included in ARIA-E Model Building (Database as of 3 March 2017)

Number of Patients (Number of Events)	Study WN25203	Study WN28745	Total	Comment
Total included in study	**797 (69)**	**371 (60)**	**1168 (129)**	
Placebo treatment	234 (2)	108 (3)	342 (5)	Excluded from model building
Database cleaning ongoing	3 (0)	—	3 (0)	Excluded from model building
Total included in study on active drug	**560 (67)**	**263 (57)**	**823 (124)**	
Long-term constant dose before titration	64 (9)	83 (17)	147 (26)	Excluded from model building
Total included into model building	**496 (58)**	**180 (40)**	**676 (98)**	
Titrated without prior treatment	24 (2)	67 [18]	91 (20)	Included in model building
Doses always smaller or equal to 225 mg	472 (56)	113 (22)	585 (78)	Included in model building

ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Table 7 ARIA-E Parameters for Gantenerumab when Applied to Titration Data

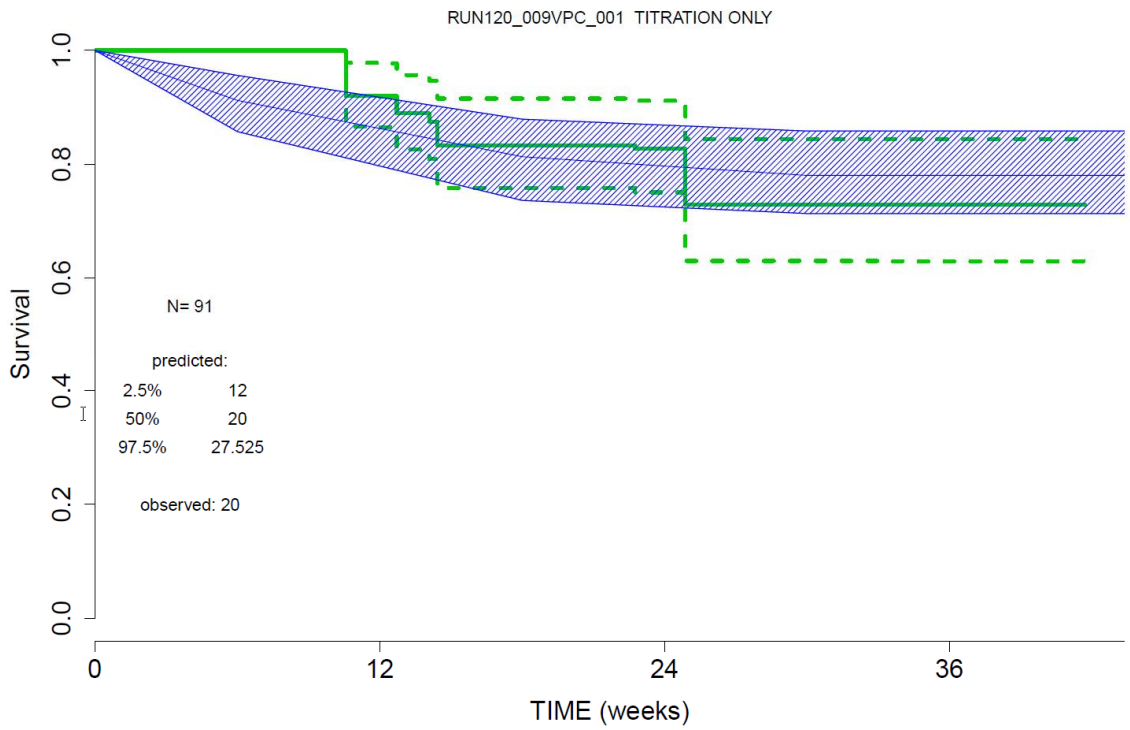
I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (μg/mL)
2.36 ± 1.01 E-5 (non-carrier) 3.75 ± 1.30 E-5 (carrier)	323.44 F	2.15 F	6.07 ± 0.702	7.75 ± 2.70

ARIA-E = amyloid-related imaging abnormality–edema/effusion; F = fixed.

Figures 5–7 show visual predictive checks for the final model. For both patients groups selected for model building, the diagnostics look acceptable (see Figures 5 and 6). For the excluded patient group who exhibited constant gantenerumab dosing followed by titration, often with 1 to 2 years of treatment gap in between, the diagnostics indicate a considerable mismatch. This could not be corrected by introducing covariates (such maximum treatment gap) into the model. It appears that the hazard model with its time component is not flexible enough for such regimens.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Figure 5 Visual Predictive Check on Titration Data Used for Model Building

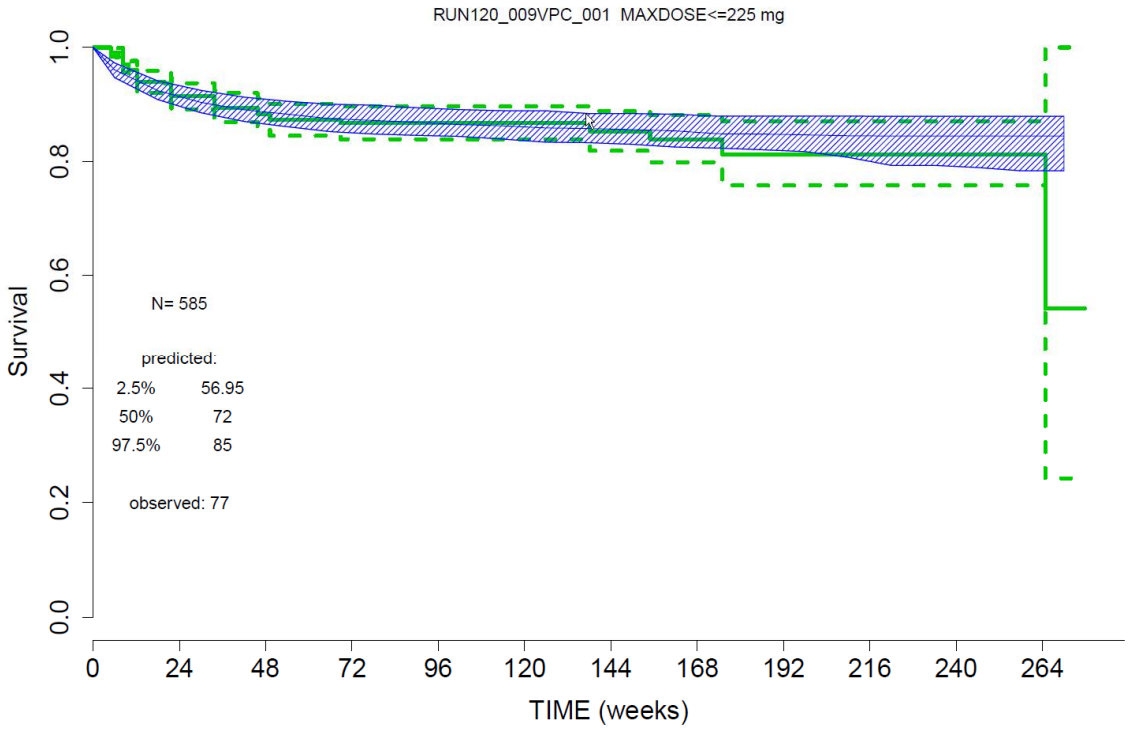


ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events (2.5%, 50% [median], and 97.5% percentiles), and the actual observed number of events. The apparent mismatch over the first 12 weeks is because no scan was performed during this period. Survival refers to the ARIA-E event-free proportion.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Figure 6 Visual Predictive Check on Data Used for Model Building (Based on Data from Patients Enrolled in the Double-Blind WN25203 and WN28745 Studies and Dosed with 225 mg)

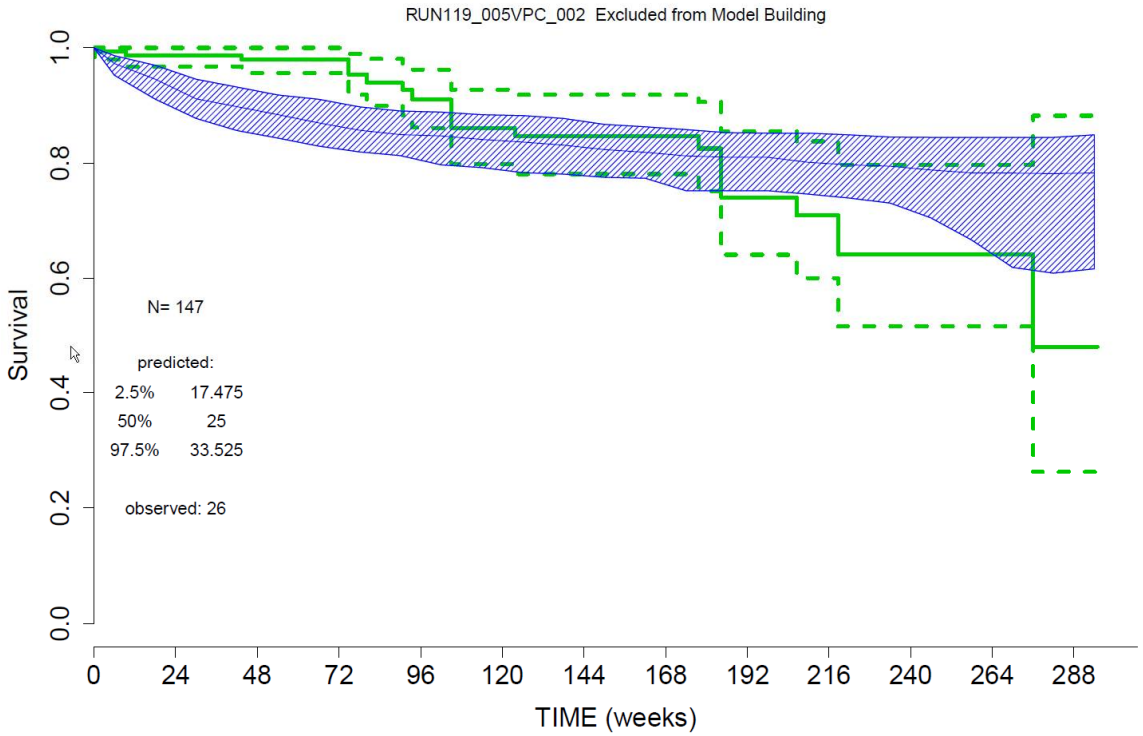


ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% (median), and 97.5%) and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Figure 7 Visual Predictive Check on Excluded Data from Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% (median), and 97.5%) and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

3.3. MODELING DATABASE AS OF 8 JULY 2017

Table 8 presents an updated ARIA-E model building using data based on the cutoff date of 8 July 2017. In Table 9, ARIA-E parameters for gantenerumab are summarized when applied to titration data.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Table 8 Patient Population Included in ARIA-E Model Building (Database as of 7 July 2017)

Number of Patients (Number of Events)	*Study WN25203*	*Study WN28745*	*Total*	*Comment*
Total included in study	***797 (75)***	***371 (60)***	***1168 (135)***	
Placebo treatment	*227 (2)*	*108 (3)*	*335 (5)*	*Excluded from model building*
Database cleaning ongoing	*2 (0)*	—	*2 (0)*	*Excluded from model building*
Total included in study on active drug	***568 (73)***	***263 (57)***	***831 (130)***	
Long-term constant dose before titration	*66 (14)*	*80 (16)*	*146 (30)*	*Excluded from model building*
Total included into model building	***502 (59)***	***183 (41)***	***685 (100)***	
Titrated without prior treatment	*36 (3)*	*70 (19)*	*106 (22)*	*Included in model building*
Doses always smaller or equal to 225 mg	*466 (56)*	*113 (22)*	*579 (78)*	*Included in model building*

ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Table 9 ARIA-E Parameters for Gantenerumab when Applied to Titration Data

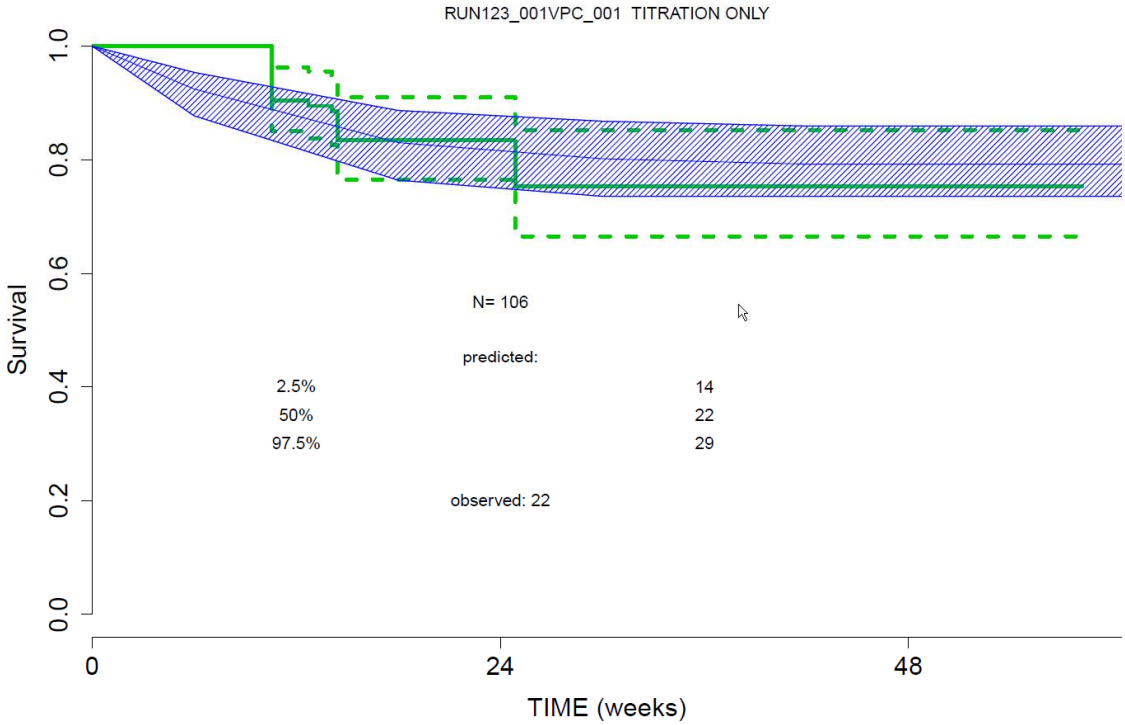
I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (µg/mL)
2.14 ± 0.9742 E-5 (non-carrier) 3.52 ± 1.24 E-5 (carrier)	323.44 F	2.15 F	5.92 ± 0.688	6.78 ± 2.88

ARIA-E = amyloid-related imaging abnormality–edema/effusion; F = fixed.

Figures 8–10 show visual predictive checks for the final model. For both patients groups selected for model building, the diagnostics look acceptable (see Figures 8 and 9). For the excluded patient group who exhibited constant gantenerumab dosing followed by titration, often with 1 to 2 years of treatment gap in between, the diagnostics indicate a considerable mismatch. This could not be corrected by introducing covariates (such maximum treatment gap) into the model. It appears that the hazard model with its time component is not flexible enough for such regimens.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Figure 8 Visual Predictive Check on Titration Data Used for Model Building

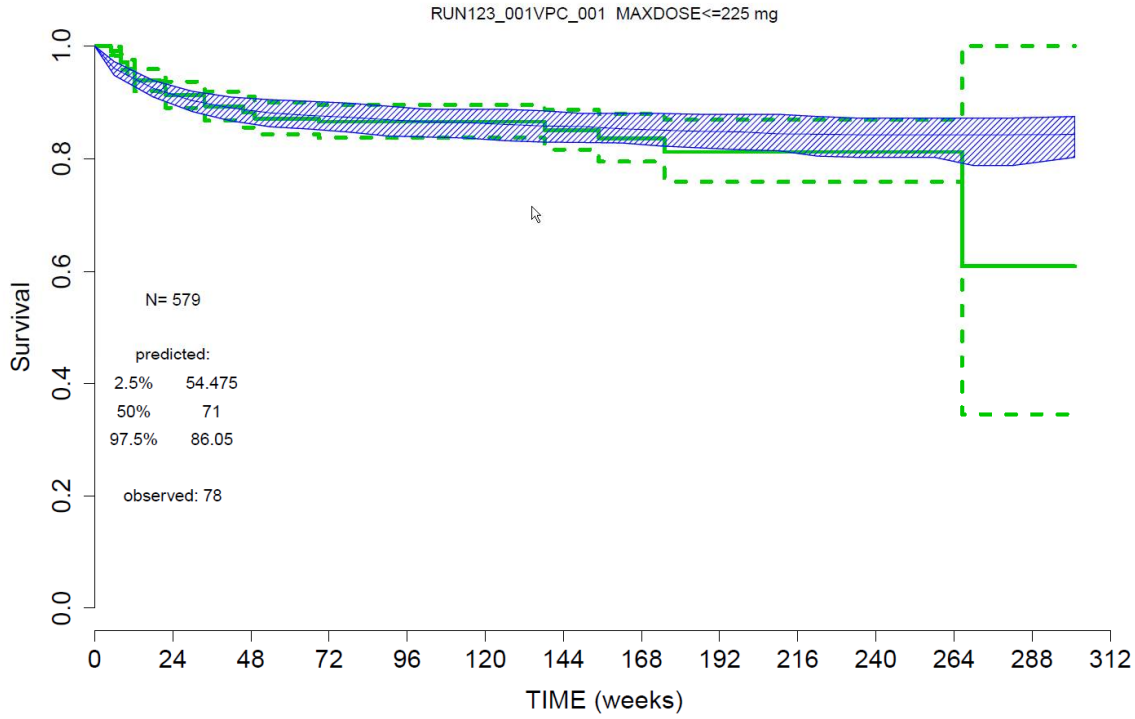


ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events (2.5%, 50% [median], and 97.5% percentiles), and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Figure 9 Visual Predictive Check on Data Used for Model Building

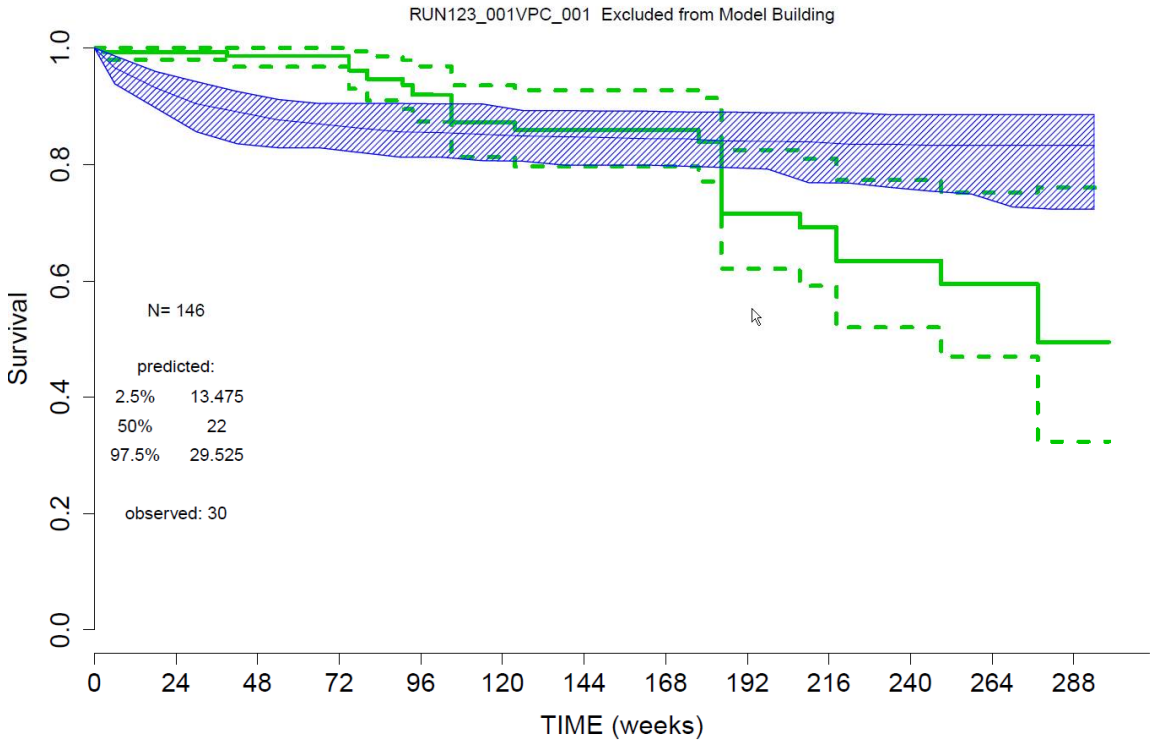


ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% (median), and 97.5%) and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Figure 10 Visual Predictive Check on Excluded Data from Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% (median), and 97.5%) and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

REFERENCES

Hutmacher M, Hu C, Guenzler-Pukall V, et al. Pharmacokinetic-pharmacodynamic modeling of amyloid-related imaging abnormalities of edema following administration of bapineuzumab to subjects with mild to moderate Alzheimer's disease [poster]. Presented at the American Conference on Pharmacometrics 2013.

Sevigny J, Chiao P, Williams L, et al. Randomized, double-blind, Phase 1b study of BIIB037 in patients with prodromal or mild Alzheimer's disease. 12th International Congress on Alzheimer's and Parkinson's Disease. Symposium 26 March 2015. Nice, France.

Appendix 6
Management *Rules* for Amyloid-Related Imaging Abnormalities

Event	Characteristics	Action to Be Taken
ARIA-E	Asymptomatic ARIA-E and BGTS <4	Continue study drug at the same dose level (i.e., do not uptitrate) and repeat MRI scan 4 weeks later. – As long as BGTS is <4 and ≥1, continue study drug at the same dose level and repeat MRI 4 weeks later. – Once ARIA resolves, resume uptitration and obtain a MRI scan per the titration schedule. For patients randomized to the Q2W regimen, perform another MRI scan 3 months after study drug reintroduction.
	Symptomatic ARIA-E (of any size) or asymptomatic ARIA-E and BGTS ≥4	Temporarily interrupt study drug and perform MRI scans at 4-week intervals until symptoms and ARIA-E resolve. When symptoms and ARIA-E resolve, reintroduce study drug at dose given at the time the event was detected. – Perform a MRI scan before next scheduled dose for patients randomized to the Q4W regimen or after the second dose for patient randomized to the Q2W regimen. – If no new ARIA-E is detected, resume uptitration and obtain an MRI per titration schedule. For patients randomized to the Q2W regimen, perform another MRI scan 3 months after study drug reintroduction.
	Any recurrence of ARIA-E	Treat the same as the first event (based on symptoms and BGTS).
ARIA-H	>15 ARIA-H cumulatively (should not include any disseminated LH)	continue study drug.

ARIA-E = amyloid-related imaging abnormality–edema/effusion; ARIA-H=amyloid-related imaging abnormality–hemosiderin deposition; BGTS=Barkhof grand total score; LH=leptomeningeal hemosiderosis; MRI=magnetic resonance imaging; Q2W=every 2 weeks.

Appendix 7
Summary of Prohibited and Conditional Concomitant Medications

Drug Class [a]	*At Screening*	*During the Study*
Active immunization (i.e., vaccination) to prevent or postpone cognitive decline	***Prohibited*** *Any prior use*	***Prohibited*** *If initiated, patient must be discontinued from the study.*
Gantenerumab	***Prohibited*** *Any prior use*	***Prohibited*** *Outside of study settings*
Passive immunization therapies (i.e., monoclonal and/or polyclonal antibodies)	***Conditional*** *Prior use is allowed if medication was discontinued at least 12 months prior to screening.*	***Prohibited*** *If initiated, patient must be discontinued from the study.*
Experimental small molecules in treatment of Alzheimer's disease with putative effect on the progression of the disease (e.g., beta-secretase inhibitors)	***Conditional*** *Prior use is allowed if medication was discontinued more than 6 months or 5 half-lives (whichever is longer) prior to screening.*	***Prohibited*** *If initiated, patient must be discontinued from the study.*
Experimental drugs with putative symptomatic benefit in Alzheimer's disease (e.g., 5HT6 antagonists, muscarinic M1 positive allosteric modulators, histamine H3 antagonists)	***Conditional*** *Prior use is allowed if medication was discontinued more than 6 months or 5 half-lives (whichever is longer) prior to screening.*	***Prohibited*** *If initiated, patient must be discontinued from the study.*

[a] *The list is not exclusive. Examples of medications may vary based on local regulations and availability.*

[b] *If condition is not met, neuropsychological battery data for the next scheduled study visit may be censured.*

[c] *Low doses for non-cancerous conditions may be allowed on a case-by-case basis upon approval of the Medical Monitor.*

Appendix 7
Summary of Prohibited and Conditional Concomitant Medications (cont.)

Drug Class [a]	*At Screening*	*During the Study*
Experimental small molecules for any other indication	***Conditional*** *Prior use is allowed if medication was discontinued more than 4 months or 5 half-lives (whichever is longer) prior to screening.*	***Prohibited*** *If initiated, patient must be discontinued from the study.*
Cholinesterase inhibitors, N-methyl-D-aspartate receptor antagonists, and medical food supplements (where approved) for cognitive impairment or Alzheimer's disease (e.g., donepezil, galantamine, rivastigmine, memantine, Axona®, Souvenaid®)	***Conditional*** *If patient is on a stable dose for at least 3 months prior to screening and there is no plan to change the dose prior to completing the baseline visit*	***Conditional*** [b] *If chronic use is initiated, patient should be on stable dose for at least 3 months prior to the next scheduled neurocognitive assessment.*
Nootropics and stimulants (e.g., amphetamine, methylphenidate preparations, aniracetam, armodafinil, modafinil, piracetam)	***Conditional*** *Prior use is allowed if medication was discontinued more than 1 month or 5 half-lives (whichever is longer) prior to screening.*	***Prohibited*** *If initiated, patient may be discontinued from the study.*
Antiplatelet therapy (e.g., aspirin, clopidogrel, dipyridamol)	***Permitted***	***Permitted***
Opiates or opioid pain medications (e.g., oxycodone, hydrocodone, codeine, morphine, fentanyl, meperidine, methadone)	***Conditional*** *Prior use is allowed if medication was discontinued at least 3 months or 5 half-lives (whichever is longer) prior to screening.*	***Conditional*** [b] *Only allowed for intermittent short-term use and must be discontinued 2 days or at least 5 half-lives (whichever is longer) prior to any neurocognitive assessment.*

[a] *The list is not exclusive. Examples of medications may vary based on local regulations and availability.*

[b] *If condition is not met, neuropsychological battery data for the next scheduled study visit may be censured.*

[c] *Low doses for non-cancerous conditions may be allowed on a case-by-case basis upon approval of the Medical Monitor.*

Appendix 7
Summary of Prohibited and Conditional Concomitant Medications (cont.)

Drug Class [a]	*At Screening*	*During the Study*
Anticoagulants (e.g., heparin, warfarin, apixaban, rivaroxaban, dabigatran, edoxaban)	***Conditional*** *Prior use is allowed if medication was discontinued at least 3 months or 5 half-lives (whichever is longer) prior to screening.*	***Prohibited*** *If chronic use is initiated, patient must be discontinued from the study.* ***Note:*** *Short-term (e.g., perioperative) use of anticoagulant medications will not result in permanent discontinuation from the study; however, the plan for anticoagulation must be discussed with the Medical Monitor prior to initiating treatment.*
Selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, serotonin modulator and stimulator antidepressants (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram, duloxetine, desvenlafaxine, venlafaxine, agomelatine, vortioxetine)	***Conditional*** *If patient is on a stable dose for at least 3 months prior to screening and there is no plan to change the dose prior to completing the baseline visit*	***Conditional*** [b] *If chronic use is initiated, patient should be on stable dose for at least 3 months prior to the next scheduled neurocognitive assessment.*
Tricyclics and tetracyclics antidepressants (e.g., amitriptyline, nortriptyline, imipramine, desiramine, maprotiline, mirtazapine)	***Prohibited*** *Any prior use for treatment of depression, anxiety, insomnia* ***Conditional*** *Prior use for treatment of pain is allowed if medication was discontinued at least 12 months prior to screening.*	***Prohibited*** *If initiated, patient may be discontinued from the study.*

[a] *The list is not exclusive. Examples of medications may vary based on local regulations and availability.*

[b] *If condition is not met, neuropsychological battery data for the next scheduled study visit may be censured.*

[c] *Low doses for non-cancerous conditions may be allowed on a case-by-case basis upon approval of the Medical Monitor.*

Appendix 7
Summary of Prohibited and Conditional Concomitant Medications (cont.)

Drug Class [a]	*At Screening*	*During the Study*
Typical and atypical antipsychotic medication (e.g., aripiprazole, chlorpromazine, clozapine, fluphenazine, haloperidol, olanzapine, quetiapine, risperidone)	***Prohibited*** *Any prior chronic use* ***Conditional*** *If used as brief treatment for a non-psychiatric indication (e.g., emesis) and treatment was discontinued at least 6 months prior to screening*	***Conditional*** [b] *Only allowed for intermittent short-term use and must be discontinued 2 days or at least 5 half-lives (whichever is longer) prior to any neurocognitive assessment.*
Barbiturates, benzodiazepines, hypnotics (e.g., zopiclone, eszopiclone, zolpidem, flurazepam, ramelteon) and anticholinergic over-the-counter sleeping aids (e.g., diphenhydramine, doxylamine)	***Conditional*** *Prior chronic use is not permitted.* *Past episodic use is allowed, if treatment was completely discontinued at least 6 months prior to screening.*	***Conditional*** [b] *Short-term, episodic use is permitted except within 3 days or at least 5 half-lives (whichever is longer) of prior to any neurocognitive assessment.*
Over-the-counter first-generation antihistamines and anticholinergic sleeping aids (e.g., carbinoxamine, clemastine, chlorpheniramine, brompheniramine, diphenhydramine, doxylamine)	***Conditional*** *Prior chronic use is not permitted.* *Past episodic use is allowed, if treatment was completely discontinued at least 6 months prior to screening.*	***Conditional*** [b] *Short-term, episodic use is permitted except within 3 days or at least 5 half-lives (whichever is longer) of prior to any neurocognitive assessment.*
Anticonvulsants (e.g., phenytoin, carbamazepine, gabapentin, acetazolamide, acetazolam, clobazam, ethosuximide, levetiracetam, topiramate, vigabatrin)	***Prohibited*** *Any prior use for treatment of epilepsy/seizure disorders* ***Note:*** *Low-dose anticonvulsants for treatment of pain are allowed.*	***Prohibited*** *If initiated, patient may be discontinued from the study.* ***Note:*** *Low-dose anticonvulsants for treatment of pain are permitted.*

[a] *The list is not exclusive. Examples of medications may vary based on local regulations and availability.*

[b] *If condition is not met, neuropsychological battery data for the next scheduled study visit may be censured.*

[c] *Low doses for non-cancerous conditions may be allowed on a case-by-case basis upon approval of the Medical Monitor.*

Appendix 7
Summary of Prohibited and Conditional Concomitant Medications (cont.)

Drug Class [a]	*At Screening*	*During the Study*
L-Dopa/carbidopa, dopamine agonists, monoamine oxidase inhibitors or other medications for Parkinson disease, Parkinson disease dementia or dementia with Lewy bodies (e.g., deprenyl, apomorphine, benzhexol, orphenadrine, selegiline, ropinirole, pramipexole)	***Conditional*** *Prior use for treatment of Parkinson disease or other neurodegenerative conditions is only permitted if treatment was discontinued at least 12 months prior to screening.* ***Note:*** *Use of dopamine agonist for treatment for restless-leg syndrome is conditionally allowed, if patient is on a stable dose for at least 3 months prior to screening and there is no plan to change the dose prior to completing the baseline visit.*	***Prohibited*** *If initiated, patient may be discontinued from the study.*
Chemotherapy drugs [c]	***Prohibited*** *Within 24 months of screening*	***Prohibited*** *If initiated, patient may be discontinued from the study.*

[a] *The list is not exclusive. Examples of medications may vary based on local regulations and availability.*

[b] *If condition is not met, neuropsychological battery data for the next scheduled study visit may be censured.*

[c] *Low doses for non-cancerous conditions may be allowed on a case-by-case basis upon approval of the Medical Monitor.*

PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP EFFICACY AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN29922
VERSION NUMBER:	5
EUDRACT NUMBER:	2017-001364-38
IND NUMBER:	102,266
NCT NUMBER:	NCT03444870
TEST PRODUCT:	Gantenerumab (RO4909832)
MEDICAL MONITOR	[redacted], *MBBS, PhD*
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
02-Aug-2021 12:03:00	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
4	*23 May 2020*
3	16 January 2020
2	11 February 2018
1	21 July 2017

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

The changes to the protocol, along with a rationale for each change, are summarized below:

- Section 1.3.5 Overall Benefit-Risk Summary has been updated to address the COVID-19 pandemic impact on the Benefit-Risk assessment for Study WN29922 as per the MHRA requirement
- Objectives and endpoints of the Double-Blind Treatment Period (Table 2) have been updated in the following manner:

– Corresponding endpoints for the 'exploratory efficacy' objective have been revised to remove 'in global outcome' as a criteria for the measurement of change from baseline to Week 116, which was added in error.

– The exploratory endpoint 'Time to clinically evident decline, defined as an increase of ≥ 2.0 in CDR-SOB subscore or ≥ 1 in at least four items of the FAQ' has been removed from Table 2, as it is not considered relevant anymore based on new available data.

– The exploratory endpoint 'Change from baseline to Week 116 measured by 'Function as assessed by the CDR function subscore" has been removed as it is no longer considered relevant based on new available data.

– The exploratory endpoint 'clinically evident decline as measured using the CDR' has been added to Table 2.

– The pharmacokinetic (PK) objective of the study has been changed to an exploratory PK objective to be consistent with the sparse PK sampling design and population modeling used to analyse the dose concentration–time data of gantenerumab. In addition, the protocol has been amended to enable early access PK, anti-drug antibodies (ADA) and pharmacodynamic (PD) biomarker samples. Early access will only be applied if there are sufficient sample data available to make an adequate assessment.

– The corresponding endpoints for the pharmacodynamic (PD) biomarker objective have been revised to clarify the duration of change as a measurement from baseline to Week 116 when assessing brain amyloid load, brain tau load and cerebral spinal fluid markers.

– The PD biomarker objective endpoint 'MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all participants ' has been reclassified as exploratory as it is no longer considered secondary based on new available data.

- Sections 3.1.1 and 4.1.3 have been updated to clarify that the open-label extension (OLE) of Study WN29922 is not applicable in countries that cannot run Study WN42171.
- Sections 4.1.2.7, 4.4.1, 4.7.2, and Appendix 1 have been revised to clarify the Medical Monitor's responsibility to review and support patient cohort management

and other protocol activities. Any reference to approval by the Medical Monitor with regards to medical decisions following enrollment has been removed from the protocol. The Principal Investigator (PI) may consult with the Medical Monitor/Sponsor for advice or clarification and may share risk factor information pertinent to the patient, but the medical decisions for the study participants are the responsibility of the PI.

- Section 4.1.3 has been amended to replace Week 104 with Week 116 (or Week 128, if applicable) which was omitted in the previous protocol amendment.
- Sections 4.6.3 and 4.6.4 have been amended to better clarify the order of assessments during the study visits
- Section 6.4.1 has been updated according to the estimand framework outlined in the ICH-E9 draft addendum with regards to the primary endpoint.
- Section 6.4.2 has been updated to remove the reference to time to event, which was included in error.
- Sections 6.4.4, 6.5 and 6.6 have been updated to clarify that a separate cut off may be necessary for PD biomarker, PK, and ADA samples to allow early access to PD biomarker samples and ensure expedient data analyses.
- Section 6.7.1 and 6.7.2 have been updated to include additional details surrounding the conduct of an interim analysis, should one be implemented.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP EFFICACY AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN29922
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NCT NUMBER:	NCT03444870
TEST PRODUCT:	Gantenerumab (RO4909832)
MEDICAL MONITOR:	[redacted], *MBBS, PhD*
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____

Principal Investigator's Signature Date

Please return the signed original of this form to the Sponsor or its designee. Please retain a signed copy of the form for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP EFFICACY AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**
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EUDRACT NUMBER:	2017-001364-38
IND NUMBER:	102,266
NCT NUMBER:	NCT03444870
TEST PRODUCT:	Gantenerumab (RO4909832)
PHASE:	Phase III
INDICATION:	Alzheimer's disease
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy and safety of gantenerumab compared with placebo in participants with early (prodromal to mild) Alzheimer's disease (AD). Specific objectives and corresponding endpoints for the study are outlined below for the double-blind treatment period and for the OLE period.

Objectives and Corresponding Endpoints for the Double-Blind Treatment Period

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of gantenerumab administered by SC injection compared with placebo	The change in global outcome from baseline (Day 1) to Week 116 [a], as measured by the CDR-SOB
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo on cognition and function	The change from baseline to Week 116 [a] in cognition and/or function, as measured by: • MMSE total score • ADAS-Cog11 and ADAS-Cog13 • Verbal Fluency Task • Coding • FAQ • ADCS-ADL total score and instrumental score
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo	The change from baseline to Week 116 [a] in the following: • Clinically evident decline *as measured using the CDR* • Severity, as assessed by the CDR Global Score • Dependence level, as derived from the ADCS-ADL score • Health-related quality of life, as assessed by the QoL-AD scale • Behavioral and neuropsychiatric symptoms of AD, as measured by the NPI-Q • Study partner burden, as assessed by the ZCI-AD scale • Elements of resource utilization, as assessed by the RUD-Lite • Health outcomes in participant and study partner, as measured by EQ-5D questionnaire

Aβ=amyloid-β; AD=Alzheimer's disease; ADA=anti-drug antibody; ADAS-Cog11=Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13=Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL=Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E=amyloid-related imaging abnormalities–edema/effusion; ARIA-H=amyloid-related imaging abnormalities–hemosiderin deposition; CDR=Clinical Dementia Rating; CDR-GS=Clinical Dementia Rating global score; CDR-SOB=Clinical Dementia Rating–Sum of Boxes; CSF=cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D=EuroQol-Five Dimensions; FAQ=Functional Activities Questionnaire; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; NPI-Q=Neuropsychiatric Inventory–Questionnaire; PET=positron emission tomography; PK=pharmacokinetic; QoL-AD=Quality of Life–Alzheimer's Disease; RUD-Lite=Resource Utilization in Dementia–Lite; SC=subcutaneous; ZCI-AD=Zarit Caregiver Interview–Alzheimer's Disease.

[a] If the double-blind treatment period is extended by a total of 24 weeks, the endpoints will be based on change from baseline to Week 128.

Objectives and Corresponding Endpoints for the Double-Blind Treatment Period (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of gantenerumab compared with placebo	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Presence of ADAs during the study relative to the presence of ADAs at baseline (in active treatment group only)
Pharmacodynamic Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo in participants with early (prodromal to mild) Alzheimer's disease	• Change from baseline *to Week 116* in brain amyloid load, as measured by amyloid PET scan in a subset of participants • Change from baseline *to Week 116* in brain tau load, as measured by tau PET scan in a subset of participants • Change from baseline *to Week 116* in cerebral spinal fluid markers of disease in a subset of participants, including, but not limited to, total tau, and phosphorylated tau
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo in participants with early (prodromal to mild) Alzheimer's disease	• Change over time in plasma *and other CSF* biomarkers • Change from baseline to Week 116 [a] in functional brain connectivity, as measured by resting-state functional MRI (where available) • Change from baseline to Week 116 [a] in integrity of white matter, as measured by DTI-MRI (where available) • *MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all participants*
Exploratory Pharmacokinetic Objective	***Corresponding Endpoint***
• *To characterize the PK profile of gantenerumab*	• *Plasma concentration of gantenerumab (administered subcutaneously) at specified timepoints*

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

[a] If the double-blind treatment period is extended by 24 weeks, the final endpoints will be based on change from baseline to Week 128.

Objectives and Corresponding Endpoints for the Open-Label Extension Period

Safety Objective	Corresponding Endpoints
• To evaluate the long-term safety and tolerability of SC gantenerumab in participants with early AD	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Presence of ADAs during the study relative to the presence of ADAs at baseline
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To assess the long-term efficacy of SC gantenerumab in participants with early AD	• The change in cognition, function and other outcomes over time, as measured by: • CDR • MMSE • ADAS-Cog11 and ADAS-Cog13 • Verbal Fluency Task • Coding • FAQ • ADCS-ADL • Health-related quality of life, as assessed by the QoL-AD scale • Behavioral and neuropsychiatric symptoms of AD, as measured by the NPI-Q • Study partner burden, as assessed by the ZCI-AD scale • Elements of resource utilization, as assessed by the RUD-Lite • Health outcomes in participant and study partner, as measured by EQ-5D questionnaire

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

Objectives and Corresponding Endpoints for the Open-Label Extension Period (cont.)

Exploratory Pharmacodynamic Biomarker Objective	Corresponding Endpoints
• To evaluate the long-term effect of SC gantenerumab in participants with early AD	• Brain amyloid load over time, as measured by amyloid PET scan in a subset of participants • Brain tau load over time, as measured by tau PET scan in a subset of participants • Cerebral spinal fluid markers of disease over time in a subset of participants, including, but not limited to, $A\beta_{1-42}$, total tau, and phosphorylated tau • MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, functional brain connectivity, integrity of white matter in all participants • Plasma markers over time *in all participants*

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

Study Design

Description of Study

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of gantenerumab in participants with early (prodromal to mild) AD.

The planned number of participants for the global enrollment phase for the study is approximately 1016 participants: randomized in a 1:1 ratio to receive gantenerumab and placebo (508 participants randomized to gantenerumab and 508 randomized to placebo). To maintain a balanced number of participants enrolled in each treatment arm and to ensure that the arms are comparable, randomization will be stratified by stage of disease (prodromal AD vs. mild AD), apolipoprotein E (*APOE)* allele status (presence vs. absence of the ε4 allele), use of AD medication (presence vs. absent), geographic region (Western Europe and Australia vs. Rest of the World vs. North America) and participation in longitudinal amyloid and tau positron emission tomography (PET) substudies. Approximately 175 centers in approximately 15 countries worldwide will participate in this study.

Participants will be selected on the basis of clinical diagnosis of probable AD (according to the National Institute on Aging/Alzheimer's Association [NIA/AA] diagnostic criteria and guidelines for AD) or prodromal AD (according to the NIA/AA diagnostic criteria and guidelines for mild cognitive impairment (MCI) due to AD). The aim of the study is to recruit approximately 50% of the participants with prodromal AD.

Eligible participants will be 50–90 years old, inclusive, must show evidence of β-amyloid pathology as indicated by the cerebral spinal fluid (CSF) tau to $A\beta_{42}$ ratio (CSF-enrolled participants) or positive amyloid PET scan by visual read (PET-enrolled participants), and meet eligibility criteria.

The study will consist of a screening period of up to 12 weeks in length following the signing of informed consent. Sites also have the option to prescreen participants on the Free and Cued Selective Reminding Test (FCSRT) and Mini-Mental State Examination (MMSE). Participants must sign a separate Informed Consent Form before administration of these tests if used for prescreening. If the results confirm a participant's eligibility, then the FCSRT and MMSE will not have to be completed again during the screening period as long as the test has been done within 12 weeks prior the baseline.

Eligible participants will then undergo baseline visit assessments (Day 1) prior to receiving the first dose of blinded study drug (gantenerumab or placebo). Participants will continue in the double-blind treatment period.

Due to the global impact of the COVID-19 pandemic and the resulting disruption in study drug administration, the duration of the double-blind treatment period will be extended by 12 weeks, with the possibility of an additional 12-week extension (for a total of 24 weeks). This may result in the following scenarios:

- Scenario 1: Participants who are enrolled and active in the double-blind treatment period after implementation of Protocol Version 4 will have the double-blind treatment period extended by 12 weeks, with the final efficacy and safety visit at Week 116.
- Scenario 2: If the COVID-19 pandemic results in greater than anticipated disruptions to study drug administration, then the Sponsor has the option to extend the double-blind treatment period by an additional 12 weeks, with the final efficacy and safety visit at Week 128. This extension will be mandatory for all patients who are active in the double-blind treatment period at the time that the extension decision is implemented.

Participants who have already had the last study drug administration at Week 102 and their final efficacy and safety visit at Week 104 and who have completed the double-blind treatment period prior to implementation of *the study extension by 12 weeks*, will continue into the OLE of either the WN29922 study or the WN42171 study. Alternatively, they will continue into the safety follow-up period.

For participants who enroll or who are active in the double-blind treatment period at the time of implementation of *the study extension by 12 weeks*, visits and study drug administration will occur Q4W until participants reach the target dose, which will be 510 mg Q2W. After the last dose of study drug (Week 114 for scenario 1 and Week 126 for scenario 2, if applicable), final efficacy and safety assessments will be performed 2 weeks later (at Week 116 for scenario 1 and at Week 128 for scenario 2, if applicable). Participants may then enroll in an OLE study if they are eligible (either in the OLE part of this study or in the WN42171 study) or have safety follow-up visits 14 and 50 weeks after the last dose for safety and limited efficacy assessments.

All participants who prematurely discontinue treatment will continue participating in the study and will be asked to return for collection of safety and limited efficacy data.

Participants will undergo brain magnetic resonance imaging (MRI) examinations for safety monitoring and longitudinal changes in brain structure. MRI scans will be read by a central MRI reader. Participants will also undergo standard tests to monitor safety (blood tests, ECG), as well as the Columbia–Suicide Severity Rating Scale (C-SSRS) to monitor for suicidality, tests for cognition, function, and quality-of-life (QoL) status. Blood samples for the assessment of PK samples, pharmacodynamic (PD) biomarkers, and ADA will be obtained from all participants.

The incidence and nature of adverse events, serious adverse events, amyloid-related imaging abnormalities–edema/effusion (ARIA-E) and ARIA–hemosiderin deposition (ARIA-H), injection site reactions (ISRs), adverse events of special interest, ECGs, and laboratory abnormalities will be assessed on a regular basis by an unblinded independent Data Monitoring Committee (iDMC).

Once the double-blind treatment period is completed, participants who consent and are eligible may opt to participate in an OLE. If the stand-alone open-label study (Study WN42171) is not open for enrollment at the time that a participant completes the double-blind treatment period of this study, then the participant will use the OLE procedures described in this study. These participants will then transition to Study WN42171 after they have completed the entire schedule of activities in the OLE of this study and the protocol for Study WN42171 is available and approved as per local requirements. If Study WN42171 is open for enrollment at the time

that a participant completes the double-blind treatment period of this study, then the participant will enroll directly in Study WN42171 and not in the OLE portion of this protocol. *The OLE of Study WN29922 is not applicable in countries that cannot run Study WN42171.*

The study consists of three distinct periods:

- Screening (including an optional prescreening): The screening period may last up to 12 weeks for each eligible participant.
- Double-blind treatment period: After screening, participants who meet all eligibility criteria will be randomly assigned to one of two arms (gantenerumab or placebo) in a 1:1 ratio. Following baseline assessments, each participant will receive a minimum of nine SC Q4W administrations of study drug (uptitration period), followed by up to 40 administrations of study drug in the double-blind treatment period in scenario 1 or up to 46 administrations in scenario 2, if applicable. The last dose of study drug will be administered at Week 114 in scenario 1 and at Week 126 in scenario 2, if applicable. At the end of the double-blind treatment period, 2 weeks after the last dose, all participants will undergo the final safety and efficacy study visit. Participants who have already completed the double-blind treatment period prior to implementation of *the study extension by 12 weeks* will have received 34 SC Q2W administrations of study drug during the double-blind treatment period. The last dose will be administered at Week 102, and their final efficacy and safety visit will be at Week 104.
- Post–double-blind treatment period: After the final efficacy and safety study visit, all participants will be asked to come back for the long-term follow-up visits or to continue in the OLE.

  Long-term follow-up: Long-term follow-up will consist of a 50-week follow-up period with evaluations at Weeks 14 and 50 after completion of study drug administration. Participants who withdraw early during the double-blind treatment period or during the OLE period are also asked to complete the long-term follow-up visits.

  OLE: All eligible participants will have the opportunity to enter an OLE study.

  – Eligible participants who enrolled early in the WN29922 study may start the OLE and will then transition to the open-label Study WN42171 (details will be provided in Protocol WN42171). Participants who terminated the WN29922 OLE early will be asked to come back for long-term follow-up visits.
  – If the WN42171 protocol is available and approved by local authorities, the remaining eligible participants will directly be enrolled in the open-label Study WN42171.

China Enrollment Plan

Based on historical data, participant recruitment is expected to take longer in China; therefore, a specific China enrollment plan has been established. Thus, if at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the National Medical Products Administration (NMPA) during the global enrollment phase, additional participants may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. All participants enrolled at NMPA-recognized sites in the global enrollment phase will be included in the primary analysis. All participants enrolled at NMPA-recognized sites in the global enrollment phase and the China extension phases will be included in a China-specific analysis. Details will be provided in the Statistical Analysis Plan (SAP).

Substudies

The substudies associated with Study WN29922 will be described in separate protocols, and participants consenting to enroll in these substudies will be asked to sign the associated Informed Consent Forms.

To date, there are two substudies associated with Study WN29922: a longitudinal Amyloid PET substudy and a longitudinal Tau PET substudy. The amyloid- and tau PET assessments will allow a longitudinal evaluation of the effect of gantenerumab on brain amyloid deposition as measured by florbetaben or flutemetamol PET radioligands and tau burden as measured by [^{18}F] GTP1 (an investigational radioligand for in vivo imaging of tau protein aggregates) in

participants with early AD. Details of any interim analyses relating to the substudies will *also* be described in the substudy protocols.

The PET data that are collected are expected to help in understanding the effects of gantenerumab on amyloid and tau pathology over time as well as the relationship between change in florbetaben/flutemetamol/[^{18}F] GTP1-PET and changes in other endpoints in the Study WN29922.

Data Monitoring Committee

The iDMC will evaluate participant safety and efficacy on a regular basis. In addition to the data defined in the iDMC Charter (e.g., the incidence and nature of adverse events, serious adverse events, adverse events of special interest, ARIA-E, ARIA-H, and ISRs), the iDMC will review all necessary cumulative data at regular intervals during the study, including efficacy when needed. It is anticipated that these assessments will occur approximately every 3 months. At the time of each review, the iDMC will make appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, the treatment regimen should be modified, the protocol should be amended, enrollment should be held pending further safety evaluations). The iDMC will also evaluate planned or unplanned interim analyses for efficacy or futility.

Decisions will be made in consideration of the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details such as the committee's composition, frequency, and timing of meetings, and members' roles and responsibilities are detailed in the iDMC Charter.

Final decisions will rest with the Sponsor.

Number of Patients

The planned enrollment specifies approximately 1016 participants.

Target Population

This study will enroll approximately 1016 participants with increased brain amyloid burden (defined according to CSF or PET criteria), objective memory impairment indicated by cognitive assessment, and a diagnosis of probable AD or prodromal AD based on relevant NIA/AA criteria during the global enrollment phase.

An increase in sample size may be considered in the event of changes to the sample size assumptions on the basis of blinded data review or factors external to the study.

If at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA during the global enrollment phase, additional participants may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. All participants enrolled at NMPA-recognized sites in the global enrollment phase will be included in the primary analysis. All participants enrolled at NMPA-recognized sites in the global enrollment phase and the China extension phases will be included in a China-specific analysis. Details will be provided in the SAP.

Inclusion Criteria

Participants must meet the following criteria for study entry:

- Ability to provide written consent signed by the participant (co-signed by the participant's legally authorized representative, if required by the local regulations, guidelines, and independent Ethics Committee or Institutional Review Board)
- Age 50–90 years old at screening, inclusive
- Availability of a person (referred to as the "study partner" throughout this protocol) who:
  - Agrees to participate throughout the duration of study
  - In the investigator's judgment, has frequent and sufficient contact (e.g., 5 times per week or approximately 10 hours per week) with the participant
  - In the investigator's judgment, is able to provide accurate information regarding the participant's cognitive and functional abilities, including knowledge about domestic activities, hobbies, routines, social skills, and basic activities of daily life; work and educational history; cognitive performance including memory abilities, language abilities,

temporal and spatial orientation, judgment and problem solving; emotional and psychological state; and can report any changes in the general health status

- Agrees to provide information and to complete all aspects of the study at clinic visits (which require partner input for scale completion)
- Signs the necessary Informed Consent Form(s), and has sufficient cognitive capacity to accurately report on the participant's behavior as well as cognitive and functional abilities
- Is fluent in the language used at the site and has sufficiently good general health to have a high likelihood of maintaining the same level of interaction with the patient and participation in study procedures throughout the duration of the study

Every effort should be made to have same study partner participate throughout the duration of the study.

- Fluency in the language of the tests used at the study site
- Willingness and ability to complete all aspects of the study (including MRI, lumbar puncture [if applicable], clinical genotyping, and PET imaging [if applicable])

  The participant should be capable of completing assessments either alone or with the help of the study partner.
- Adequate visual and auditory acuity, in the investigator's judgment, sufficient to perform the neuropsychological testing (eye glasses and hearing aids are permitted)
- Evidence of AD pathological process, as confirmed by CSF tau/$A\beta_{42}$ or on amyloid PET scan by qualitative read by the core/central PET laboratory
- Demonstrated abnormal memory function at screening (FCSRT cueing index ≤ 0.67 and free recall ≤ 27)
- Screening MMSE score ≥ 22 and CDR-GS of 0.5 or 1.0
- Probable AD dementia (consistent with NIA/AA core clinical criteria for probable AD dementia) or prodromal AD (consistent with the NIA/AA diagnostic criteria and guidelines for mild cognitive decline due to AD)
- If the participant is receiving symptomatic AD medications, a stable dosing regimen for at least 3 months prior to screening and until randomization
  - Participants receiving GV-971 or who are planning to take GV-971 during the study are not eligible
- Agreement not to donate blood or blood products for transfusion for the duration of the study and for 1 year after final dose of study drug
- Agreement not to participate in other research studies for the duration of this trial and its associated substudies
- For enrollment in the China extension, participants must have residence in mainland China, Hong Kong, or Taiwan and be of Chinese ancestry
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 16 weeks after the last dose of study drug

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

Exclusions Related to Central Nervous System Disorders

Participants who meet any of the following criteria related to CNS disorders will be excluded from study entry:

- Any evidence of a condition other than AD that may affect cognition, including, but not limited to, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, Parkinson disease, corticobasal syndrome, Creutzfeldt-Jakob disease, progressive supranuclear palsy, frontotemporal lobar degeneration, Huntington disease, normal pressure hydrocephalus, seizure disorder, delirium or hypoxia
- History or presence of clinically evident systemic vascular disease (e.g., clinically significant carotid/vertebral artery stenosis or plaque, aortic aneurysm), that in the opinion of the investigator has the potential to affect cognitive function
- History or presence of clinically evident cerebrovascular disease (e.g., intracranial or cerebral vascular malformations, aneurysm, intracranial macrohemorrhage)

  Participants with asymptomatic developmental venous anomalies may be eligible after discussion with and approval by the Medical Monitor.
- History or presence of posterior reversible encephalopathy syndrome
- History or presence of any stroke with clinical symptoms within the past 12 months, or documented history within the last 6 months of an acute event that is consistent, in the opinion of the investigator, with a transient ischemic attack
- History of severe, clinically significant (persistent neurologic deficit or structural brain damage) CNS trauma (e.g., cerebral contusion)
- History or presence of intracranial mass (e.g., glioma, meningioma) that could potentially impair cognition
- Presence of infections that affect brain function or history of infections that resulted in neurologic sequelae (e.g., HIV, syphilis, neuroborreliosis, and viral or bacterial meningitis and encephalitis)
- History or presence of systemic autoimmune disorders that potentially cause progressive neurologic disease with associated cognitive deficits (e.g., multiple sclerosis, lupus erythematosus, anti–phospholipid antibody syndrome, and Behçet disease)
- History of schizophrenia, schizoaffective disorder, major depression, or bipolar disorder

  History of major depression is acceptable if participant has had no episode within the past year or is considered in remission or depression is controlled by treatment.
- At risk for suicide in the opinion of the investigator
- Alcohol and/or substance abuse or dependence (according to the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, Version 5) within the past 2 years

  Nicotine use is allowed.

  Marijuana use is not allowed and must be discontinued at least 3 months before screening.

Imaging-Related Criteria

Participants who meet any of the following imaging criteria will be excluded from study entry:

- According to the MRI central reader, MRI evidence of any of the following:
  - $>$ 2 lacunar infarcts
  - Any territorial infarct $>$ 1 cm^3
  - Any white matter lesion that corresponds to an overall Fazekas score of 3 that requires at least one confluent hyperintense lesion on the fluid-attenuated inversion recovery (FLAIR) sequence, which is $\geq$ 20 mm in any dimension

- Combined number of microbleeds and areas of leptomeningeal hemosiderosis (i.e., cumulative ARIA-H) on MRI more than five (and should not include any disseminated leptomeningeal hemosiderosis) based on the review performed by the central reader prior to randomization
- Presence of any other significant cerebral abnormalities, including ARIA-E, as assessed on MRI
- Inability to tolerate MRI procedures or contraindication to MRI, including, but not limited to, presence of pacemakers not compatible with MRI, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan, or any other clinical history or examination finding that, in the judgment of the investigator, would pose a potential hazard in combination with MRI

Cardiovascular Disorders

Participants who meet any of the following criteria related to cardiovascular disorders will be excluded from study entry:

- History or presence of clinically symptomatic atrial fibrillation requiring maintenance therapy

  Participants who experienced non-valvular atrial fibrillation that resolved more than 1 year ago and was not associated with prior stroke are eligible.
- Within the last year, unstable or clinically significant cardiovascular disease (e.g., myocardial infarction)

  Heart failure classified as New York Heart Association Class I or II cardiac disease is allowed if not associated with hospitalization within the previous 12 months.
- Uncontrolled hypertension (e.g., blood pressure generally >160 mmHg systolic or >95 mmHg diastolic)

Hepatic and Renal Disorders

Participants who meet any of the following criteria related to hepatic and renal disorders will be excluded from study entry:

- Chronic kidney disease, indicated by creatinine clearance <30 mL/min to be calculated by the central laboratory using the Cockcroft-Gault formula at screening, which remains <30 mL/min if retested
- Confirmed and unexplained impaired hepatic function as indicated by screening AST or ALT $\geq 3\times$ the upper limit of normal (ULN) or total bilirubin $\geq 2\times$ ULN

Infections and Immune Disorders

Participants who meet any of the following criteria related to infections and immune disorders will be excluded from study entry:

- History of, or known to currently have HIV infection, or hepatitis B or hepatitis C infection that has not been adequately treated in the opinion of the investigator, or history of spirochete infection of the CNS (e.g., syphilis, Lyme disease, or borreliosis)
- Systemically, clinically significantly immunocompromised participants, owing to continuing effects of immune-suppressing medication

Metabolic and Endocrine Disorders

Participants who meet any of the following criteria related to metabolic and endocrine disorders will be excluded from study entry:

- Abnormal thyroid function as indicated by abnormal screening tests that are judged to be clinically significant by the investigator, or abnormal thyroid function that requires a new treatment or an adjustment of current treatment

  A participant may be rescreened if there is no improvement in cognition in the investigator's judgment after 3 months of adequate treatment for thyroid function.

- Participants with evidence of folic acid deficiency (as indicated by folic acid level below the lower limit of normal) or vitamin B-12 deficiency (as indicated by vitamin B-12 level below the lower limit of normal and/or methylmalonic acid levels above ULN)

  A participant may be rescreened if there is no improvement in cognition after 3 months of adequate treatment for folic acid or vitamin B-12 deficiency.
- Screening hemoglobin A_{1c} (HbA_{1C}) $>$ 8% (retesting is permitted if slightly elevated) or poorly controlled insulin-dependent diabetes (including hypoglycemic episodes)

  A participant may be rescreened after 3 months to allow optimization of diabetic control.

Exclusions Related to Medications

The following medications are prohibited for a pre-specified duration prior to study start, as indicated, and during the entire period of study participation (participants who start these medications during the study may be withdrawn from study treatment):

- Any previous administration of gantenerumab or active immunotherapy (vaccine) that is being evaluated to prevent or postpone cognitive decline
- Any passive immunotherapy (immunoglobulin) or other long–acting biologic agent that is under evaluation to prevent or postpone cognitive decline within 1 year of screening
- Any other investigational treatment or any other treatment with a monoclonal antibody within 5 half-lives or 4 months prior to screening, whichever is longer
- Any previous administration of GV-971
- Any previous treatment with medications specifically intended to treat Parkinson symptoms or any other neurodegenerative disorder within 1 year of screening and with no plans to initiate such medications prior to randomization

  Certain medications are acceptable if the participant is taking the medicine for a non-neurodegenerative disorder, such as restless leg disorder (e.g., pramipexole).
- Typical antipsychotic or neuroleptic medication within 6 months of screening and with no planned changes prior to randomization except as brief treatment for a non-psychiatric indication (e.g., emesis)

  Atypical antipsychotic medications are not allowed except for intermittent short-term use and will need to be discontinued 2 days or at least 5 half-lives (whichever is longer) prior to any neurocognitive assessment.
- Anticoagulation medications within 3 months of screening with no plans to initiate any prior to randomization

  Anti-platelet treatments (e.g., aspirin, clopidogrel, and dipyridamol) are permitted.

  Short-term, perioperative use of anticoagulant medications will not result in permanent discontinuation from the study; however, *for* any such use *it is recommended to* prospectively *seek* advice from the Medical Monitor and temporary study drug interruption *may be required*.
- Chronic use of opiates or opioids (including long-acting opioid medication) within 3 months of screening with no plans to initiate any prior to randomization

  Intermittent short-term use of short–acting opioid medications for pain is permitted except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.
- Stimulant medications (amphetamine, methylphenidate preparations, or modafinil) within 1 month of screening and throughout the study
- Chronic use of benzodiazepines, barbiturates, or hypnotics from 3 months before screening and with no plans to initiate any prior to randomization

  Intermittent short-term use of benzodiazepines, buspirone, or short-acting hypnotic medication for sleep or anxiety is allowed except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

Other Exclusions

Participants who meet any of the following criteria will be excluded from study entry:

- Other causes of intellectual disability that may account for cognitive deficits observed at screening (e.g., static encephalopathy, closed brain injury, mental retardation)

  This may be based on, for example, the participant's sufficient education or work experience.
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study
- Deformity of the lumbosacral region of the spine that in the opinion of the investigator would contraindicate lumbar puncture in participants who will have lumbar puncture
- Clinically significant abnormal screening blood, CSF (if applicable), or urine results that remain abnormal at retest
- Impaired coagulation (screening prothrombin time [PT] $> 1.2 \times$ the ULN that remains abnormal on retest)
- History of cancer, with the following exceptions:
  - If considered to be cured
  - If not being actively treated with anti-cancer therapy or radiotherapy and, in the opinion of the investigator, is not likely to require treatment in the ensuing 5 years
  - For prostate cancer or basal cell carcinoma, no significant progression over the previous 2 years
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins, including gantenerumab
- Hypersensitivity to any of gantenerumab excipients
- Any other severe or unstable medical condition that, in the opinion of the investigator or Sponsor, could be expected to progress, recur, or change to such an extent that it could put the participant at special risk, bias the assessment of the clinical or mental status of the participant to a significant degree, interfere with the participant's ability to complete the study assessments, or would require the equivalent of institutional or hospital care
- Residence in a skilled nursing facility such as a convalescent home or long-term care facility: Participants who subsequently require residence in such facilities during the study may continue in the study and be followed for efficacy and safety, provided that they have a study partner who meets the minimum requirement

Eligibility for the Open-Label Extension

Participants who have been randomized and who have completed the double-blind treatment period will be eligible to participate in the OLE, provided they do not meet any of the following criteria:

- Discontinued from study treatment during the double-blind treatment period.
- Received any other investigational medication during the double-blind treatment period or after the end of double-blind treatment.
- Participation in the OLE deemed inappropriate by the investigator (e.g., any serious medical condition or other concerns that preclude the participant's safe participation in the OLE or ability to comply with the required procedures).
- Presence of ARIA-E findings at the Week *116 (or Week 128, if applicable)* MRI scan (participants who have ongoing ARIA-E findings at the Week *116 [or Week 128, if applicable]* will stay in the double-blind treatment period until the finding is deemed resolved). *For those participants who enroll into the GRADUATE OLE from Week 104, before the double-blind extension took place, eligibility for the OLE would be based on the Week 104 scan.*

End of Study

The end of the study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for safety analyses or safety follow-up is received for the last participant, whichever occurs later.

Length of Study

The study will consist of a screening period of up to 12 weeks (including the optional prescreening period) for each eligible participant who signs the Informed Consent Form and agrees to participate, followed by a double-blind treatment period of study drug treatment plus a visit 2 weeks after the last dose. The duration of the double-blind treatment period is extended by 12 weeks (116 weeks in total in scenario 1). In case scenario 2 is implemented, the double-blind treatment period will be extended by 24 weeks (128 weeks in total in scenario 2, if applicable). For participants not entering the OLE period, this will be followed by the post–double-blind treatment period of two follow-up visits at 14 and 50 weeks after the last dose. Thus, for a participant not entering the OLE period, the maximum length of study is approximately 176 weeks in scenario 1 or 188 weeks in scenario 2 (if applicable).

For participants entering the OLE period, the extension will consist of an open-label period of at least 35 weeks. If a participant is ready to be uptitrated to the target dose and if the safety MRI allows, the participant will then be transitioned to the WN42171 open-label study. If there is an ongoing ARIA-E, the participant will remain in Study WN29922 until the ARIA-E resolves and the participant is ready to be uptitrated to the target dose. In case the dosing is temporarily interrupted for any other reason, the participant will be kept in the WN29922 study until they are ready to be uptitrated to the target dose. Participants who are not willing to transition to the WN42171 open-label study after OLE Week 35 will be asked to come back for two follow-up visits at 14 and 50 weeks after the last dose (OLE Follow Up 1 and Follow Up 2, respectively).

Investigational Medicinal Products

The investigational medicinal product (IMP) for this study is gantenerumab.

Test Product (Investigational Drug)

Gantenerumab or placebo will be administered by SC injection to all participants.

Double-Blind Treatment Period

Gantenerumab will be administered by SC injection to all patients randomized to the active treatment arm, regardless of *APOE* ε4 status, at a dose of 120 mg SC Q4W for 3 months, 255 mg SC Q4W for 3 months, and 510 mg SC Q4W for 3 months, prior to reaching the target dose. Once the target dose is reached, study drug will be administered every 2 weeks (Q2W administration of 510 mg SC gantenerumab). The switch to a Q2W administration schedule allows decreasing the number of SC administrations in the abdomen per visit.

Note: A minimum of 3 doses during each dosing step must be administered prior to uptitration.

For Q4W injections, a time window of ±7 days is allowed for dosing visits. For Q4W injections, the recommended minimum time between doses is 3 weeks. The maximum recommended time between doses should not exceed 6 weeks. Once study drug is administered Q2W, the time window for dosing visits is ±3 days. For Q2W injections, the recommendation is not to administer more than 1020 mg (i.e., 2 times 510 mg Q2W) within 28 days. Always return to the initial planned schedule per randomization for subsequent visits.

Regardless of dose, each participant will undergo up to a total of 49 dosing visits in scenario 1 or 55 dosing visits in scenario 2 (if applicable) in the double-blind treatment period of the study. Participants who have completed the double-blind treatment period at the time of the implementation of *the 12 week study extension*, will have undergone up to 43 dosing visits. Injections will be administered as one 0.8-mL (120-mg dose), one 1.7-mL (255-mg dose), or two 1.7-mL injections (510-mg dose) subcutaneously to the abdomen, respectively.

Placebo of identical composition (except protein) and identical volume to gantenerumab will be administered by SC injection to all participants randomized to placebo at the same frequency and using the same route of administration.

On study drug administration days that include efficacy assessments, study drug must be administered at the clinical site. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

At applicable sites, study drug may be administered by a trained nursing professional at the participant's home or another suitable location, if the participant has given written informed consent to participate in home nursing visits.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Open Label Extension Period

During the OLE, participants previously randomized to the active treatment arm will continue to be administered the study drug every two weeks (Q2W administration of 510 mg SC gantenerumab). Participants previously randomized to the placebo arm will be required to undergo 9 months of uptitration.

In order to maintain the previous study treatment blinding (Sponsor, site, and participant), all participants will be dosed every two weeks in the OLE. As in the double-blind treatment period, a safety MRI has to be performed before each uptitration to ensure that the participant can be uptitrated safely to the next dose.

To ensure blinding to previous treatment, administration will consist of one 0.8-mL and two 1.7-mL injections for the 120-mg dose or will consist of two 1.7-mL injections for the 255 mg dose and 510-mg dose. Injections will be administered subcutaneously to the abdomen.

Note: As in the double-blind part, a minimum of 3 doses during each dosing step must be administered prior to uptitration. During uptitration in the OLE, a minimum of 3 doses of each dosing step also have to be administered prior to be eligible for uptitration. In the OLE, a dose is defined as two consecutive dosing visits (one with an even dose number and one with an odd dose number).

For the OLE, the time window for dosing visits is $\pm$ 3 days. Always return to the initial planned schedule per randomization for subsequent visits.

Participants enrolled in the WN29922 OLE study will have to complete the full titration scheme (i.e., at least 12 weeks on each dosing step) prior to being able to enroll in the WN42171 open-label study where they will receive 510 mg SC Q2W.

On study drug administration days that include efficacy assessments (see the schedule of activities in Appendix 1), study drug must be administered at the clinical site. Study personnel who prepare and administer the study drug must not be involved with any efficacy assessments or safety evaluations.

At applicable sites, study drug may be administered by a trained nursing professional at the participant's home or another suitable location if the participant has given written informed consent to participate in home nursing visits.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

PET Tracers

All participants who are enrolled in PET substudies will be assessed by PET imaging using an appropriate PET ligand. For screening, the possible amyloid PET ligands will be florbetapir, florbetaben, and flutemetamol. According to E.U. guidance, the PET tracers as used in the context of this study, are designated as non-IMP. In some regions, according to local regulations, these PET tracers may be considered to be IMP.

In countries where the PET radioligands are approved for marketing, the approved local product information will be provided, and in countries where they are not approved for marketing, the Investigator’s Brochures will be provided.

Details about the PET substudies are described in separate protocols.

Statistical Methods

Primary Analysis

The primary efficacy outcome measure is the change in CDR-SOB from baseline (Day 1) to Week 116. In the case where the double-blind treatment period is extended for an additional 12

weeks, the primary efficacy outcome measure will be the change in CDR-SOB from baseline (Day 1) to Week 128.

The clinical question of interest is to assess the study treatment effect on disease progression up to Week 116 (or Week 128, if applicable), irrespective of use or initiation of symptomatic treatments for AD, in the absence of the COVID-19 pandemic.

In accordance with the estimand framework outlined in the ICH-E9 addendum (EMA 2018), the attributes of the estimand for the primary endpoint are defined as follows:

- *Population: early (prodromal to mild) AD population including all randomized participants.*
- *Variable: change from baseline at Week 116 (or Week 128) in the CDR-SOB.*

  Treatment: prescribed study drug including uptitration to the target dose, irrespective of use or initiation of symptomatic treatment for AD.
- *Intercurrent events (ICE): the list of ICE will be defined in the SAP, this includes:*

  Treatment discontinued for study drug or condition–related (SDCR) reasons (e.g., treatment-related adverse event or lack of efficacy):

  Treatment discontinued for non-study drug or condition–related reasons (NSDCR) reasons (e.g. purely administrative reason).
- *Population level summary: mean change from baseline to Week 116 (or Week 128, as appropriate) between gantenerumab-treated participants and placebo-treated participants.*

The primary estimand is a combination of a treatment-policy strategy and a hypothetical strategy (FDA 2017) to account for the different assumptions for each type of ICE. Full details of the primary estimand, and of the corresponding estimator and estimation methods (e.g. statistical model, multiple imputation for missing or excluded data points) will be provided in the SAP. Supplementary estimands may also be considered and will be defined in the SAP.

Every effort will be made to minimize missing data. Furthermore, the Sponsor *has made* every effort to expedite the implementation of *the 12 week extension to the double-blind treatment period*. If the study is extended by an additional 12 weeks (for a total extension of 24 weeks), the number of patients in scenario 1 (who will have missing Week 128 efficacy data) will be minimized.

Participants who discontinue early from study treatment will be asked to return for collection of safety and limited efficacy data (i.e., the primary and secondary efficacy endpoints) until the end of the double-blind treatment period and follow-up visits. To explore the robustness of MMRM results for the primary efficacy conclusions sensitivity analyses (e.g., using multiple imputation and pattern mixture models) will be performed. Descriptive summaries of the number of participants with missing data, the number of participants in each scenario, the timing, and reasons for discontinuation from the study will also be provided by treatment group.

Determination of Sample Size

Determination of sample size is based on participants enrolled in the global enrollment phase. In this study, approximately 1016 participants will be enrolled and randomized in 1:1 ratio to each treatment arm (gantenerumab or placebo) during the global enrollment phase. A sample size increase may be considered if factors external to the study or blinded study data review would warrant a change to the sample size assumptions.

Additional participants may be randomized during the China extension if at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA during the global enrollment phase.

The estimated sample size required to demonstrate efficacy with regard to CDR-SOB is based on the following assumptions:

- The mean change in the CDR-SOB from baseline to Week 104 is 2.5 points in the placebo arm
- A common standard deviation across treatment arms for change of approximately 2.97 from baseline to Week 104 in the CDR-SOB
- Gantenerumab has a true effect of a 30% relative reduction in deterioration of CDR-SOB

Based on these assumptions, and using a student's T-test with equal variance, a sample size was calculated for 90% power to detect a true treatment effect of 30% relative reduction in deterioration of CDR-SOB at a two-sided α of 0.05.

Uncertainties on parameters affecting the power (e.g., dropout rate, study drug discontinuation rate, standard deviation, and placebo decline) were assumed to be equivalent to a drop-in sample size of up to around 35% and were corrected for accordingly. This calculation leads to a total of 1016 participants in the study.

At the date of writing Protocol Version 4, it is expected that participants *would have missed* an average of 8 weeks of study drug administration over the course of the original 2-year study due to the COVID-19 pandemic. This has the potential to decrease the power of the study from ~90% to ~80%. To mitigate the impact of missed administrations, the double-blind treatment period *was* extended by 12 weeks. Under current assumptions, this brings the study power back to the originally planned ~90%.

The sample size may be increased from 1016 up to 1322 participants (661 participants per arm). The decision whether to increase sample size will be based on blinded study data review, e.g., by a review of the frequency of missed study drug administrations due to the COVID-19 pandemic. Further details will be described in the SAP. The assessment will be performed by the Sponsor at a specified timepoint. The sponsor will remain blinded. The sample size will not be reduced on the basis of this assessment. Other factors external to the study may also trigger a decision to increase sample size.

Interim Analyses

Optional Futility Analysis

The Sponsor may perform an interim analysis for futility approximately 116 weeks after 50% of the targeted study enrollment has been reached. If the study is extended by an additional 12 weeks, the interim analysis will be performed approximately 128 weeks after 50% of the targeted study enrollment has been reached. The exact timing of an interim analysis may be synchronized with Study WN39658.

An independent data coordinating center will be responsible for the interim analyses. The study results will only be reviewed by the iDMC and the Sponsor will remain blinded. Other third party vendors may be involved in data preparation and analyses, as appropriate.

The iDMC may recommend to stop for futility if the failure criterion is met. The failure criterion will represent a low probability of a positive study outcome given the data observed at the time of interim analysis. *If the futility criteria are not met, the study continues beyond the interim analysis. The failure criterion will be pre-specified in the iSAP.*

Details of the futility analysis, including the final decision to conduct it, the rationale, timing, and statistical details for the analyses (such as the data that would be reviewed by the iDMC and futility thresholds) will be documented in the iSAP. This will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.

Optional Interim Analyses

Based on availability of information pertaining to gantenerumab or other compounds with similar mode of action that may emerge during the course of this study, the Sponsor may choose to conduct an additional interim analysis *which may include* efficacy*, safety and biomarker outcomes including amyloid PET SUVr and/or other biomarkers to confirm PD effect. This analysis may be done on a whole study population or in a well predefined subgroup when approximately 50% of the overall population has reached Week 116. If the study is extended by an additional 12 weeks, the interim analysis will be performed once approximately 50% of the overall population has reached Week 128.*

An independent data coordinating center will be responsible for the interim analyses. The study results will only be reviewed by the iDMC and the Sponsor will remain blinded. Other third party vendors may be involved in data preparation and analyses, as appropriate.

The iDMC may indicate that a pre-specified success criterion has been met. If so, the Sponsor may decide to present the data to a health authority. Any interim, unblinded data will be strictly firewalled to ensure those involved in the conduct of the ongoing trial and the WN42171 OLE trial remain fully blinded. If needed, appropriate measures will be taken to control the overall Type I error rate and described in the SAP.

Details of the interim analyses, including the decision to conduct the optional interim analysis, the rationale, timing, and statistical details for the analyses (such as the data that would be reviewed by the iDMC and futility or efficacy thresholds) will be documented in the SAP, and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Aβ	amyloid-beta
AD	Alzheimer's disease
ADA	anti-drug antibody
ADAS-Cog11	Alzheimer's Disease Assessment Scale–Cognition, Subscale 11
ADAS-Cog13	Alzheimer's Disease Assessment Scale–Cognition, Subscale 13
ADCS-ADL	Alzheimer's Disease Cooperative Study Group–Activities of Daily Living
ADL	activities of daily living
APOE ε4	apolipoprotein E, allele ε4
ARIA	amyloid-related imaging abnormality
ARIA-E	amyloid-related imaging abnormality–edema/effusion
ARIA-H	amyloid-related imaging abnormality–hemosiderin deposition
AUC	area under the concentration–time curve
AUC_{inf}	area under the concentration–time curve from Time 0 to infinity
BOLD	blood oxygenation level-dependent
BGTS	Barkhof grand total score
CDR	Clinical Dementia Rating
CDR-GS	CDR global score
CDR-SOB	Clinical Dementia Rating–Sum of Boxes
C_{max}	maximum concentration
CNS	central nervous system
COA	clinical outcome assessment
CRO	contract research organization
CSF	cerebral spinal fluid
C-SSRS	Columbia–Suicide Severity Rating Scale
CT	computed tomography
CTAD	Clinical Trials in Alzheimer's Disease
DTI	diffusion tensor imaging
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
EQ-5D	EuroQol-Five Dimensions questionnaire

Abbreviation	Definition
FA	fractional anisotropy
FA	fractional anisotropy
FAQ	Functional Activities Questionnaire
FCSRT	Free and Cued Selective Reminding Test
FCSRT-IR	Free and Cued Selective Reminding Test–Immediate Recall
FDA	(U.S.) Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
GRE	gradient recalled echo
HbA_{1C}	hemoglobin A_{1c}
HIPAA	Health Insurance Portability and Accountability Act
HN	home nursing
ICE	intercurrent event
ICH	International Council on Harmonisation
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ISR	injection-site reaction
ITT	intent to treat
IWG	International Working Group
IV	intravenous
IxRS	interactive voice or Web-based response system
LPLV	last patient, last visit
MAD	multiple-ascending dose
MCI	mild cognitive impairment
MMRM	mixed model repeated measure
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NIA/AA	National Institute on Aging/Alzheimer's Association
NMPA	National Medical Products Administration
NPI-Q	Neuropsychiatric Inventory–Questionnaire
NSDCR	non-study drug or condition-related
OLE	open-label extension
PD	pharmacodynamic
PET	positron emission tomography
PK	pharmacokinetic

Abbreviation	Definition
PT	prothrombin time
p-tau	phosphorylated tau
QoL	quality of life
QoL-AD	Quality of Life–Alzheimer's Disease
Q2W	every 2 weeks
Q4W	every 4 weeks
RBR	Research Biosample Repository
rs-fMRI	resting-state functional magnetic resonance imaging
RUD-Lite	Resource Utilization in Dementia–Lite
SAD	single-ascending dose
SAP	Statistical Analysis Plan
SC	subcutaneous
SDCR	study drug or condition-related
SOB	Sum of Boxes
SUVr	standardized uptake value ratio
t-tau	total tau
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing
ZCI-AD	Zarit Caregiver Interview–Alzheimer’s Disease

1. BACKGROUND

1.1 BACKGROUND ON ALZHEIMER'S DISEASE

The World Health Organization estimates that around 50 million people worldwide are diagnosed with dementia and that there are 10 million new cases every year. The total number of people with dementia is estimated to reach 82 million in 2030 and will more than triple by 2050 to 152 million. AD is the most common form of dementia, accounting for 60%–70% of cases (World Health Organization 2017). The prevalence of AD increases with age, with a global prevalence of 5%–8% in people 60 years and older. Because of its increasing prevalence, long duration, and high cost of care, AD is expected to continue to represent a major public health problem for decades to come.

There is great inter-individual variability in AD progression with survival dependent on many factors, including age at onset. In general, the clinical picture evolves from "predementia" or "prodromal AD" to mild, moderate, and then severe AD. At the early stage of AD, a slight impairment of memory, language, and visuospatial function can be observed. As AD advances, patients become progressively impaired and the burden on caregivers significantly increases. The median survival time following a diagnosis of AD strongly depends on the patient's age at diagnosis and ranges from 8.3 years for persons diagnosed with AD at 65 years old to 3.4 years for those 90 years old (Brookmeyer et al. 2002). On average, individuals live 3–9 years after diagnosis (Helzner et al. 2008) and some survive as long as 20 years.

It is well recognized that in comparison to other therapeutic domains, there is a real unmet medical need in AD therapy (Gauthier et al. 2016). To date, only five medications have received marketing approval to treat the symptoms of AD, including acetylcholinesterase inhibitors (AChEi) and N-methyl-d-aspartate receptor antagonists. These approved drugs are recognized to temporarily improve some clinical symptoms of AD in some patients but do not modify progression of the disease (Cummings et al. 2016). Recent efforts have mostly focused on therapies targeting amyloid (Bachurin et al. 2017) as these offer the most compelling therapeutic targets (Graham et al., 2017). These therapies are based on the amyloid hypothesis that posits amyloid-β (Aβ) accumulation as the primary factor driving Aβ pathogenesis (Selkoe 1991; Hardy and Selkoe 2002; Selkoe and Hardy 2016). This Aβ accumulation in the brain begins well before the development of clinical dementia in AD and causes a series of downstream events leading to synaptic dysfunction, inflammation, neurodegeneration, and clinical symptoms. For these reasons, treatments that prevent, slow, or decrease the accumulation of brain Aβ are being tested as therapeutic agents in AD.

Preclinical evidence has suggested that monoclonal Aβ antibodies may be able to remove and reduce deposition of Aβ aggregates from the brain. In transgenic animal models of AD, vaccination with Aβ or passive immunization with anti–Aβ antibodies resulted in decreased amyloidosis and in improvement of memory function in some transgenic models cognitive function (Janus et al. 2000). Accumulating clinical evidence

also supports that monoclonal Aβ antibodies can bind Aβ and promote its clearance (Salloway et al. 2009; Ostrowitzki et al. 2012), reduce deposition of Aβ aggregates, and reduce markers of neurodegeneration in the CSF (Roche Research Report No. 1066251). In a Phase I study, reduction of deposited amyloid as shown on brain amyloid PET imaging was associated with a time and dose-related slowing of cognitive decline (Sevigny et al. 2016). Because the neurological changes associated with AD develop decades before clinical symptoms emerge, it is thought that earlier intervention may be more effective in arresting or delaying disease progression (Sevigny et al. 2016). Consequently, therapies targeting this process have the potential to significantly alter the progression of the disease. Gantenerumab, a fully human monoclonal antibody targeting aggregated forms of Aβ-like Aβ oligomers, fibrils, and plaques, is expected to address this need (Bohrmann et al. 2012).

1.2 BACKGROUND ON GANTENERUMAB

Gantenerumab (or RO4909832) is a fully human anti−Aβ peptide antibody developed by in vitro selection utilizing aggregated Aβ and in vitro maturation within a complete human Igγ, subclass-1 framework (IgG1). Gantenerumab recognizes a conformational epitope of Aβ present in aggregated Aβ and that is demonstrated for both major species of Aβ that is, $Aβ_{1-40}$ and $Aβ_{1-42}$. Gantenerumab has a molecular mass of 146.3 kDa. In vitro, gantenerumab recognizes synthetic aggregated Aβ fibrils and Aβ oligomers with high nanomolar affinity (K_D, ~0.6−1.2 nM). Based on additional in vitro studies and studies in animal models, the pharmacologic profile suggests that in humans, gantenerumab may prevent, inhibit, and reduce accumulation of Aβ, which is believed to play an important role in the pathogenesis of AD.

Gantenerumab is manufactured by cell culture of a recombinant Chinese hamster ovary−K1 mammalian cell line and subsequent purification of the antibody. The gantenerumab drug substance manufacturing was optimized during development, leading to several manufacturing processes (G1, G2, and G3). Recently, the gantenerumab manufacturing process was further optimized from G3 to G4 to improve process robustness and increase overall process yield. Drug material manufactured by G4 process is used in Phase III clinical trials (e.g., Study WN29922). Gantenerumab is in clinical development for patients with early (prodromal to mild) AD and is also being investigated in carriers of familial AD mutations (DIAN-TU) (Bateman et al. 2017).

Refer to the gantenerumab Investigator's Brochure for details on nonclinical and clinical studies.

1.2.1 Nonclinical Studies

1.2.1.1 Nonclinical Pharmacology

The binding characteristics of gantenerumab were engineered to achieve specific and highly sensitive recognition of the assembly structure of aggregated human $Aβ_{1-42}$ and $Aβ_{1-40}$ peptides, which are major components in Aβ plaques. Specificity was

demonstrated ex vivo for genuine human Aβ plaques in AD brain slices. The minimum effective concentration for staining of human Aβ plaques is 10 ng/mL (0.07 nM).

Gantenerumab showed a concentration-dependent increase in cellular phagocytosis of human Aβ plaques by human primary cells like microglia and differentiated macrophages in a brain-slice phagocytosis assay. The measured minimal effective concentration of 10 ng/mL (0.07 nM) is consistent with the observed efficacy for human Aβ plaque binding.

In single-dose and multiple-dose studies, effective brain penetration and binding to Aβ plaques in vivo were demonstrated in various models of AD-related amyloidosis, such as the PS2APP transgenic mouse model. Gantenerumab showed significant and accumulative binding to Aβ plaques. The data indicate that there is no requirement for continuous high peripheral levels to achieve a sustained binding of gantenerumab to amyloid plaques.

The plaque binding of gantenerumab from several manufacturing processes has been evaluated. The degree of plaque binding for gantenerumab manufactured by the G1 and G2 processes was investigated by semi-quantitative fluorescence imaging and was comparable in a 2-week IV safety study in PS2APP transgenic mice at doses of 0, 2, 10, and 40 mg/kg every 3 days.

An additional study, which compared the plaque binding of gantenerumab from the G3 and G4 manufacturing processes following single IV administration to PS2APP transgenic mice at a dose level of 40 mg/kg and assessed by semi-quantitative fluorescence imaging after 7 days, indicated slightly increased target engagement of the G4 material consistent with observed differences in exposure (see Section 1.2.1.2).

Chronic treatment with gantenerumab showed significant efficacy by halting progression of amyloidosis in transgenic PS2APP, APP_{London}, and tau PS2APP mouse models of AD. Amyloid reduction was evident by prevention of new plaque formation and removal of preexisting amyloid plaques by engaging microglia cells.

1.2.1.2 Nonclinical Pharmacokinetics and Metabolism

The pharmacokinetics of gantenerumab were studied in mice, rats, and cynomolgus monkeys following IV administration. Gantenerumab pharmacokinetics were characterized by a rapid initial decrease in plasma levels during the first 24 hours, followed by a long half-life, ranging from 4 to 13 days in all species. Overall, the studies demonstrate that gantenerumab has PK properties similar to other IgGs.

The pharmacokinetics of gantenerumab were also studied following SC administration in cynomolgus monkeys and mice. In cynomolgus monkeys, maximum plasma levels were reached after 3 days. The average bioavailability was estimated at 76%.

Gantenerumab was shown to penetrate the brain in both the monkey and mouse. Brain penetration in the monkey was evident from analysis of CSF samples. The CSF to plasma ratios ranged from 0.006% to 0.018%. Penetration and binding to $A\beta_{1-42}$ plaques in the mouse brain were evident from immunostaining for gantenerumab of brain sections obtained from PS2APP mice dosed with gantenerumab.

Rat PK studies have been conducted to compare the pharmacokinetics of gantenerumab derived from different manufacturing processes (G1, G2, G3, and G4).

Following IV administration to rats, the pharmacokinetics of the G1 and G2 materials were similar. The area under the concentration–time curve (AUC) of the G2 material was slightly lower and accounted for about 80% of the of the G1 material. Although standard bioequivalence criteria for AUC were not met, the observed difference in AUC was not considered to have an impact on the use of the G2 material in further clinical development as the difference in AUC is small. The average terminal half-life of both materials was comparable (8.0 and 8.8 days for the G1 and G2 materials, respectively).

A study comparing the pharmacokinetics of gantenerumab derived from the G3 and G4 manufacturing processes showed that the AUC of G3 material (used in the ongoing Phase III OLE Studies WN25203 and WN28745) was lower compared with the G4 material that will be used in Study WN29922 (mean±SD: 932±196 and 1270±187 (μg• hr/mL)/(mg/kg), respectively. The average terminal half-life of both materials was similar (11.5 and 12.3 days for G3 and G4 materials, respectively).

1.2.1.3 Toxicology and Safety Pharmacology

Potential adverse effects in relation to the presence and destruction of $A\beta_{1-42}$ plaques were assessed in PS2APP transgenic mice that were treated with up to 375 mg/kg/wk of IV gantenerumab for up to 26 weeks. No evidence of inflammatory reaction in general or other adverse effects were observed in these studies. Decreases in neutrophils and protein (albumin) that were not considered adverse were seen in mice. As a compensatory response, myeloid hyperplasia in the bone marrow was inconsistently detected in some animals. The reason for the low neutrophil counts is unclear but may be a mouse-specific effect of gantenerumab on neutrophils. Indeed, no such finding was observed in long-term nonclinical (murine and monkey) and clinical studies, and there have been no symptoms indicating immunosuppression in either species.

In cynomolgus monkeys, gantenerumab was well tolerated in repeat-dose IV toxicity studies of 13 and 26 weeks in duration (3, 10, and 20 mg/kg) and in SC toxicity studies of 13 weeks in duration (20 mg/kg) and 39 weeks in duration (up to 375 mg/kg). In the 26-week toxicity study, in which gantenerumab was administered once weekly, one male monkey in Group 2 (3 mg/kg) was found dead 24 hours after receiving the 26th dose (Day 177). The death was not considered to be related to gantenerumab treatment but rather to a bacterial infection detected on histopathology. There was no

treatment-related effect on hematologic parameters (i.e., neutrophil counts) in studies in cynomolgus monkeys.

In the absence of any adverse treatment-related effect in the 39-week toxicity study, a no-observed-adverse-effect level of 375 mg/kg/wk was established, which correlated with a mean maximum concentration (C_{max}) of 2535 μg/mL (male and female animals combined) and a mean area under the concentration–time curve from Time 0 to 168 hours ($AUC_{0-168hr}$) of 386,000 μg • hr/mL (male and female animals combined).

Reproductive toxicity studies in transgenic PS2APP mice did not reveal an effect of gantenerumab on fertility, embryo–fetal, or post-natal development.

1.2.2 Clinical Studies

Gantenerumab has been investigated in 10 completed Phase I clinical studies: three single-ascending dose (SAD) studies (BN18726, JP22474, and BP30042) of healthy volunteers and patients with mild to moderate AD, two multiple-ascending dose (MAD) studies (NN19866 and JP22431) of patients with mild to moderate AD, and three bioavailability studies of healthy subjects (one comparing the IV and SC formulations of gantenerumab [Study WP22461], two comparing lyophilized and high-concentration liquid formulations of gantenerumab [Studies WP27951 and BP29113]). In addition, a tolerability study comparing the pain between faster and slower SC administrations of gantenerumab has been completed (Study WP39322).

In order to assess suitability of the G4 material for future Phase III studies, an extended analytical comparability program was conducted followed by the nonclinical studies. Since differences were observed in AUC, a human relative bioavailability study (WP40052) comparing G3 and G4 gantenerumab after SC administration has also been conducted.

A total of 543 subjects have participated in the Phase I studies; of these participants, 406 healthy volunteers and 101 patients with AD have received gantenerumab.
Two Phase III studies designed to examine efficacy and safety of gantenerumab in patients with prodromal AD (Study WN25203) and mild AD (Study WN28745) have been converted to OLE studies. The OLE studies examining the safety and tolerability of higher doses of gantenerumab in prodromal AD (Study WN25203) and mild AD (Study WN28745) are ongoing.

Results of relevant studies are summarized below. Refer to the Gantenerumab Investigator's Brochure for further information.

In addition, gantenerumab is being investigated in the Dominantly Inherited Alzheimer Network Trial, a Phase II/III study sponsored by the Washington University School of Medicine, examining the safety, tolerability, biomarker status, and efficacy of gantenerumab (as measured by cognition) in patients who are known to have an AD-causing mutation and are therefore at risk for developing AD dementia.

1.2.2.1 Study NN19866

In the MAD study (NN19866), a total of 60 patients (34 males and 26 females) diagnosed with mild to moderate probable AD received multiple IV doses of gantenerumab (doses ranging from 6 mg to 20 mg, 60 mg, and 200 mg) or placebo every 4 weeks (Q4W) for up to 7 months. Owing to amyloid-related imaging abnormalities (ARIAs), or ARIAs of “vasogenic edema” (ARIA-E) and of “hemosiderosis or microbleeds” (ARIA-H), on brain magnetic resonance imaging (MRI) scans that occurred in some patients after two to four doses of 200 mg of gantenerumab in Cohort 4 (200 mg IV Q4W gantenerumab [equivalent to 330 mg SC Q4W] or placebo), it was decided to terminate dosing for all patients on 9 June 2008. The findings resolved spontaneously within 1–4 months after discontinuation of gantenerumab and no patient required treatment.

1.2.2.1.1 Study NN19866: Pharmacodynamic Results in the NN19866-PET Substudy

In a PET substudy of Study NN19866 (NN19866-PET), the effects of gantenerumab on amyloid load in the brain (defined as standardized uptake value ratio [SUVr] of a cortical composite volume of interest over mean cerebellum gray and using ^{11}C-PiB PET) were evaluated in 18 patients (4 in the placebo group, 8 in the 60-mg IV gantenerumab dose group, and 6 in the 200-mg IV gantenerumab dose group) after 6 months. A mean decrease of 14.9% from baseline was observed in the 200-mg gantenerumab dose group, while an increase was seen in the placebo group (mean, 20.9%), with relative stability compared with baseline in the 60-mg group (mean, 5.3%) (Ostrowitzki et al. 2012).

1.2.2.2 Study WN25203

Based on the results from Study NN19866 and from a relative bioavailability Study WP27951, the doses of 105 mg SC Q4W (equivalent to 60 mg IV Q4W) and 225 mg SC Q4W (equivalent to 130 mg IV Q4W) were selected for Study WN25203.
Study WN25203 was initially designed as a Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of 105 mg and 225 mg of gantenerumab administered subcutaneously Q4W in prodromal AD after 2 years of treatment. Randomization was based on apolipoprotein E, allele ε4 (*APOE* ε4) status. Selection of gantenerumab doses was largely driven with the objective of reducing risk of MRI findings (in the context of the clinical understanding of ARIAs at the time of study design) and by pharmacodynamic (PD) results in the MAD Study NN19866. Study WN25203 enrolled 799 patients, and 797 patients were treated (the safety-evaluable population). Following a planned interim futility analysis when

approximately 50% of patients had completed 2 years of treatment, the study was declared futile and dosing with the originally selected doses (105 mg and 225 mg) was suspended in December 2014. The mean duration of double-blind treatment was 1.73 years.

Safety analyses confirmed ARIAs and injection-site reactions (ISRs) (associated with SC administration) as identified risks of gantenerumab (see Section 1.2.3 for more details). Approximately 90% of patients experienced at least one adverse event, with the incidence comparable between treatment arms. The incidence of serious adverse events was 19.5%, 17.3%, and 16.9% in the placebo, 105-mg gantenerumab, and 225-mg gantenerumab groups, respectively (Ostrowitzki et al. 2017).

Subsequently, the trial has been converted into an OLE study evaluating doses of up to 1200 mg (see Section 1.3.1).

1.2.2.3 Study WN28745

Study WN28745 was initially designed as a Phase III, 2-year, double-blind, placebo-controlled, efficacy, and safety study of gantenerumab in approximately 1000 patients with mild AD. Patients randomized to receive gantenerumab were to follow a slow titration scheme independent of *APOE*-ε4 genotype, starting at 105 mg of SC gantenerumab Q4W for the first 24 weeks, with progression to 225 mg, based on acceptable results of the control MRI scan. Enrollment into the double-blind phase of the study was stopped in November 2015 because of the futility of Study WN25203. When Study WN28745 was stopped, 389 patients had been enrolled and 387 patients had been treated. There were 108 patients who were also enrolled in a PET substudy of brain amyloid imaging (Study WN28745-PET).

In the double-blind phase of Study WN28745, gantenerumab was found to be safe and well tolerated by patients with mild AD. Adverse events were reported for 80.5% of patients in the placebo group and for 82.8% of patients in the gantenerumab groups, respectively. The most commonly reported adverse events across all treatment groups included fall (8.5%), nasopharyngitis (7.5%), headache (7.0%), dizziness (5.7%), ARIA-E (5.4%), and back pain (5.4%). ISRs, ARIA-E, and ARIA-H were reported more commonly in patients in the gantenerumab group than in the placebo group (ISR: 8.3% vs. 1.0%; ARIA-E: 9.4% vs. 1.5%; ARIA-H: 6.3% vs. 4.1%).

Following the WN25203 futility analysis, the study was converted to an OLE study, evaluating the safety and tolerability of gantenerumab at higher doses (up to 1200 mg).

1.2.2.4 OLE Studies WN25203 and WN28745

Additional analyses of Study WN25203 results indicated that higher doses of gantenerumab may achieve clinically relevant effects on cognition and function (see Section 1.3.1). Thus, both Studies WN25203 and WN28745 were converted to OLE

studies to provide participants, including those in the placebo group, the opportunity for treatment with higher doses of gantenerumab expected to have a clinically meaningful effect. Doses up to 1200 mg SC Q4W of G3 gantenerumab are being tested, using dosing regimens designed to minimize the risk of ARIAs and taking into account the *APOE* genotype and the previous double-blind treatment and dose.

As of 1 May 2019, 383 patients had been enrolled in the OLE Studies WN25203 and WN28745, with 363 patients exposed to G3 gantenerumab doses higher than 225 mg (i.e., more than the highest repeat dose previously tested in AD patients) and 309 patients having reached the OLE target 1200-mg dose. ISRs and ARIAs remain the identified risks for gantenerumab. Continuous monitoring of safety data and MRI findings by the Sponsor has not identified any new safety signal in these ongoing studies. These OLE studies will be ending in 2020, and patients will be provided with an option to enroll in an open-label, rollover study to evaluate the safety and tolerability of long-term administration of gantenerumab (WN41874).

1.2.2.5 Study WP40052

A total of 114 healthy male and female subjects received a single dose of 600 mg of gantenerumab high concentration, liquid formulation (containing gantenerumab manufactured by either G3 or G4 process, N = 57 in each treatment group). The results showed that the plasma exposure in terms of area under the concentration–time curve from Time 0 to infinity (AUC_{inf}) was approximately 1.18 fold higher after SC administration of material manufactured by G4 process compared with material manufactured by G3 process, whereas C_{max} was similar (1.05 fold higher after administration of G4 material). Single-dose SC administration of 600 mg of gantenerumab as G3 or G4 material was safe and well tolerated.

Refer to the Gantenerumab Investigator's Brochure for details on clinical studies.

1.2.3 Safety Overview

Nonclinical characterization of gantenerumab did not show any relevant safety findings. To date, ARIAs and ISRs are the identified risks for gantenerumab. No differences between active and placebo groups have been observed in laboratory parameters, physical and neurological examinations, vital signs, or electrocardiogram (ECG) parameters.

Amyloid-Related Imaging Abnormalities

In the double-blind phase of Study WN25203 (prodromal AD), ARIA events were time, dose, and *APOE* ε4 allele status dependent. The incidence of ARIA-E was 0.8% in the placebo, 6.6% in the 105-mg gantenerumab, and 13.5% in the 225-mg gantenerumab groups. For ARIA-H, the incidence was 13.2% in the placebo, and 22.9% and 16.2% in the 105-mg and 225-mg gantenerumab treatment groups, respectively. The rates of new ARIA-E were highest between 3 and 6 months of treatment (3.8% and 7.5% in the 105-mg and 225-mg gantenerumab groups, respectively) and decreased substantially after

the first year of treatment (incidence of up to 2.3% in the 225-mg gantenerumab group in approximately 2 years). The median MRI Barkhof grand total score (BGTS) (Barkhof et al. 2013) of these findings was 3. Most ARIA events were asymptomatic and did not lead to clinically significant consequences. A total of 5 patients (1.8%) from the 105-mg gantenerumab arm and 6 patients (2.3%) from the 225-mg gantenerumab arm experienced symptoms related to ARIA findings; the most commonly reported symptom was headache (5 patients). Other symptoms reported with ARIA-E included visual disturbances (left eye diplopia and upper left quadrantanopia), focal seizure (dysarthria/aphasia that lasted for 10 minutes), anxiety, hyperreflexia, confusional state, disturbance in attention, cognitive disorder, malaise, and dizziness. Symptomatic ARIAs were of mild severity and were non-serious except for one serious adverse event of focal seizure.

Following the futility analysis for Study WN25203, treatment in the double-blind phase was discontinued in July 2017 (median double-blind treatment duration: 68 weeks) and consenting patients transitioned into OLE.

In the double-blind phase of Study WN28745, the frequency of ARIA-E was 1.5% and 11.5% in the placebo and gantenerumab groups, respectively. The frequency of ARIA-H was 11.8% and 15.1% in the placebo and gantenerumab groups, respectively. The median BGTS of ARIA-E was 3. Most ARIAs were asymptomatic and did not lead to clinically significant consequences. Two patients reported CNS adverse events as symptoms of ARIAs: one patient (0.5%) in the placebo group reported irritability that was mild in intensity and non-serious, and one patient (0.5%) in the gantenerumab group reported headache that was moderate in intensity and non-serious.

The WN25203 and WN28745 OLE studies are ongoing and consequently, data are still accruing. As of 1 May 2019, all 154 patients dosed with gantenerumab in the WN25203 OLE study had a post-baseline MRI scan. Of 154 patients, 47 (30.5%) had new ARIA-E (median maximum BGTS of 7.0), and 14 of 154 patients (9.1%) had new ARIA-H without ARIA-E. The majority of ARIA-E findings were asymptomatic, with 11 out of 47 patients with new ARIA-E MRI findings reporting associated CNS adverse events. The CNS adverse events were mostly mild to moderate in intensity, non-serious, and did not require permanent cessation of study treatment. Most symptomatic ARIA-E cases resolved with protocol-defined ARIA management rules. In 3 of the 11 patients with ARIA-E MRI findings who reported associated CNS adverse events, the events were reported as serious (confusional state, seizure, and epilepsy).

As of 1 May 2019, 219 of 225 patients dosed with gantenerumab in the WN28745 OLE study had a post-baseline MRI scan. Seventy-one of 219 patients (32.4%) had new ARIA-E (median maximum BGTS of 9.0), and 24 of 219 patients (11.0%) had ARIA-H without ARIA-E. The majority of ARIA-E events were asymptomatic, with 18 of 71 patients with ARIA-E MRI findings reporting associated CNS adverse events. The CNS adverse events were mostly mild to moderate in intensity, non-serious, did not

require permanent cessation of study treatment, and resolved with protocol-defined ARIA management rules. In 4 of the 18 patients with symptomatic ARIA-E, the events were reported as serious (ischemic stroke, generalized tonic-clonic seizure, epilepsy, and hemiplegia).

Overall, gantenerumab uptitration is associated with a lower rate of ARIA than the predicted rate for fixed dose, and the ARIA-E incidence observed in the OLEs has been in the expected range and in alignment with the ARIA-E PK/PD model. ARIAs are clinically manageable by protocol-defined MRI monitoring and dose intervention algorithms.

Injection-Site Reactions

In the double-blind phase of Study WN25203, the incidence of ISRs was 4.5%, 18.8%, and 23.1% in the placebo, 105-mg gantenerumab, and 225-mg gantenerumab groups, respectively. All ISRs were non-serious, and the majority were mild in intensity and resolved without treatment. The most common signs and symptoms of ISRs included injection-site erythema, pruritus, and rash. Two patients (0.3%) discontinued study treatment due to ISR.

In the double-blind phase of Study WN28745, the incidence of ISRs was 1.0% and 9.4% in the placebo and gantenerumab groups, respectively. All ISRs were non-serious and mild in intensity; the vast majority resolved without treatment. The most common signs and symptoms of ISRs included injection-site erythema, pruritus, hemorrhage, and rash. No patients discontinued study treatment due to ISR.

As of 1 May 2019, ISRs have been reported in 56 of 154 (36.4%) patients dosed with gantenerumab in the WN25203 OLE study, and 45 of 154 (29.2%) patients have had recurrent ISRs. All ISRs were non-serious and mild, and the majority resolved without treatment. Overall, 3 of 56 (5.4%) patients who had an ISR received treatment, which included topical steroids and antihistamines.

As of 1 May 2019, ISRs have been reported in 86 of 225 (38.2%) patients treated with gantenerumab in the WN28745 OLE study and 58 of 225 (25.8%) patients have had recurrent ISRs. All ISRs were non-serious, with the majority being mild and resolving without treatment. Overall, 9 of 86 (10.5%) patients who had an ISR received treatment, which included topical steroids and antihistamines. One patient (0.3%) experienced a severe event (injection-site pain after receiving a 600 mg dose via a pump, resulting in dose modification [i.e., uptitration was delayed]); this ISR resolved within 24 hours.

The Sponsor performs regular reviews of OLE Studies WN25203 and WN28745 data and, to date, has not identified any new or unexpected safety findings.

For safety data from all studies, refer to the Gantenerumab Investigator’s Brochure.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Currently, approved therapies for AD focus on symptomatic approaches that target synaptic function and cognitive enhancement (Cummings 2004). However, the amyloid hypothesis suggests that overproduction of Aβ or failure to effectively clear this peptide contributes to AD (Selkoe and Hardy 2016) and that accumulation of Aβ peptides is one factor contributing to AD progression (Sun et al. 2015). Thus, the targeting of Aβ and subsequent displacement of Aβ from the brain is a rational approach to modify AD progression.

Despite compelling results in AD animal models (Wisniewski and Goñi 2014), clinical success with passive immunization targeting brain amyloid in global Phase III trials remains an unachieved goal. It has been suggested that lack of sufficient target engagement of anti-amyloid antibodies has been a factor in the failure of these Phase III studies (Cummings et al. 2016). An important advancement for therapies targeting aggregated amyloid was provided based on data from the Phase Ib PRIME study of aducanumab (Biogen) (Sevigny et al. 2016).

Aducanumab is a fully human IgG1 monoclonal antibody with similar PK and PD properties as gantenerumab that binds to aggregated target fibrillary and oligomeric forms of Aβ through microglia-mediated clearance of amyloid plaques (Sevigny et al. 2016). The results from the PRIME study showed that monthly IV injections of aducanumab for 1 year led to a dose- and time-dependent reduction of amyloid plaques in the brain. In addition, in patients with early (prodromal to mild) AD, a slowing of clinical decline, as measured on the Clinical Dementia Rating–Sum of Boxes (CDR-SOB) and MMSE scores, has also been observed providing support to the hypothesis that Aβ plaque reduction confers clinical benefit.

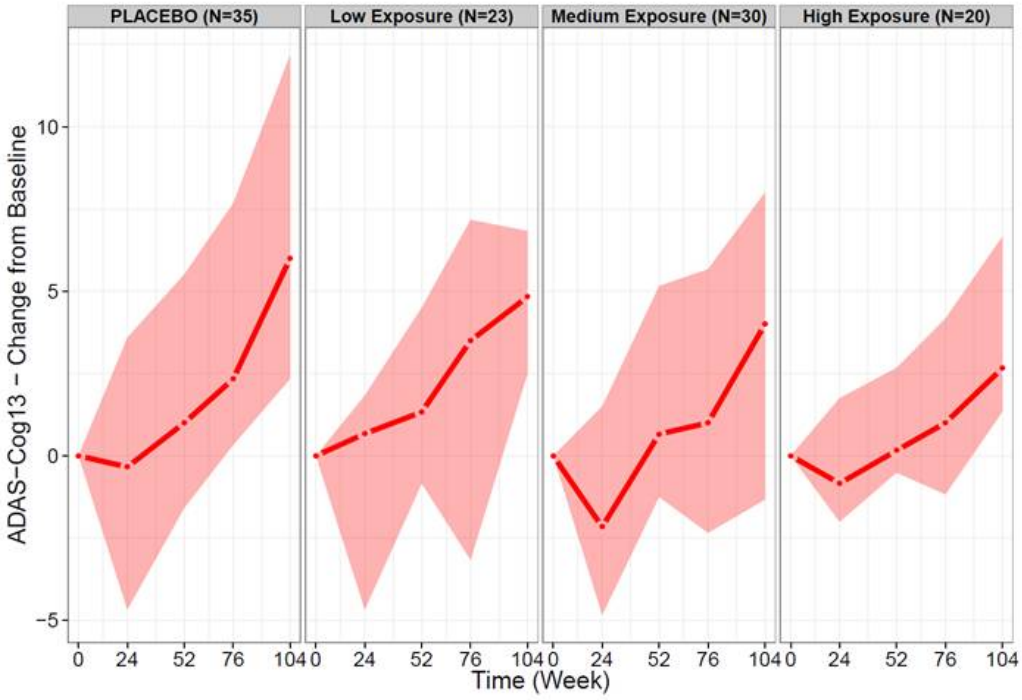
1.3.1 Study Rationale

The results of the preplanned futility analysis of data from approximately 300 patients in Study WN25203 revealed the low likelihood for trial success with the original doses studied. Indeed, no significant differences were observed on any cognitive or functional measures (i.e., CDR-SOB, MMSE, Alzheimer Disease Assessment Scale–Cognition, Subscale 13 [ADAS-Cog13], and Functional Activities Questionnaire [FAQ]) or in a subgroup analysis of baseline characteristics (demographics, cognitive, CSF biomarkers, disease severity, or *APOE* ε4 allele status). Additional post-hoc analyses indicated that the overall rate of clinical decline was lower than expected for this study population (and with higher-than expected proportion of “slow progressors”) and strongly suggested that the doses studied in Study WN25203 (105 and 225 mg) were subtherapeutic and that a higher gantenerumab dose may have a clinically relevant effect (Ostrowitzki et al. 2017).

Results of the post-hoc analyses of patients who were predicted to be progressors using a model derived from the Alzheimer’s Disease Neuroimaging Initiative data

(Delor et al. 2013) showed a drug concentration-dependent effect on clinical decline present for the ADAS-Cog13, MMSE, and Cambridge Neuropsychological Test Automated Battery results. Figure 1 displays the effects on increasing plasma gantenerumab concentrations (three concentration groups) on ADAS-Cog13 decline over the 2-year study. Greater concentrations of gantenerumab were associated with less clinical decline.

Figure 1 ADAS-Cog13 Treatment Response by Plasma Concentration: Two-Year Completing Fast Progressors in Study WN25203

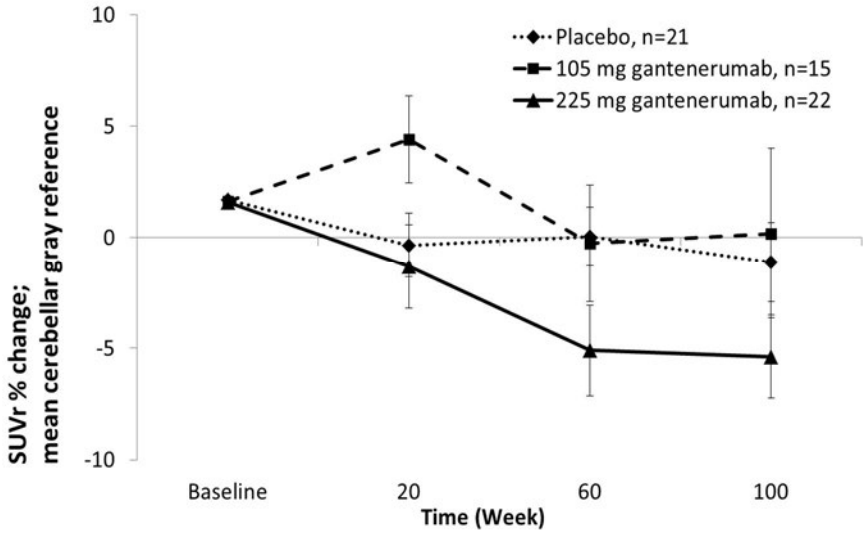


ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13.
Notes: low exposure = 1.48–5 μg/mL; medium exposure = 5–10 μg/mL;
high exposure = 10–26.68 μg/mL. Line = median; shaded = 50% observations.

Furthermore, a PET substudy of Study WN25203 using [^{18}F] florbetapir confirmed a reduction in brain amyloid in gantenerumab-treated patients in a larger, less-impaired patient sample compared with Study NN19866, which had also demonstrated reduced accumulation of brain amyloid. Time-dependent reductions in SUVr were observed in patients treated with 225 mg of gantenerumab compared with placebo using the composite cortical SUVr and reference region of mean cerebellar gray. Week 100 results showed the mean percent change from baseline in SUVr was −1.09%, 0.72%, and −4.82% in the placebo, 105-mg gantenerumab, and 225-mg gantenerumab groups, respectively (see Figure 2). A small number of patients (n = 8) continued to receive 225 mg of gantenerumab for approximately 3 years (Week 156). Analysis suggested that the effect on SUVr reduction was continuous over time because SUVr reductions

observed with the 225-mg dose of gantenerumab relative to placebo increased with the duration of long-term exposure, suggesting a sustained effect with continued exposure.

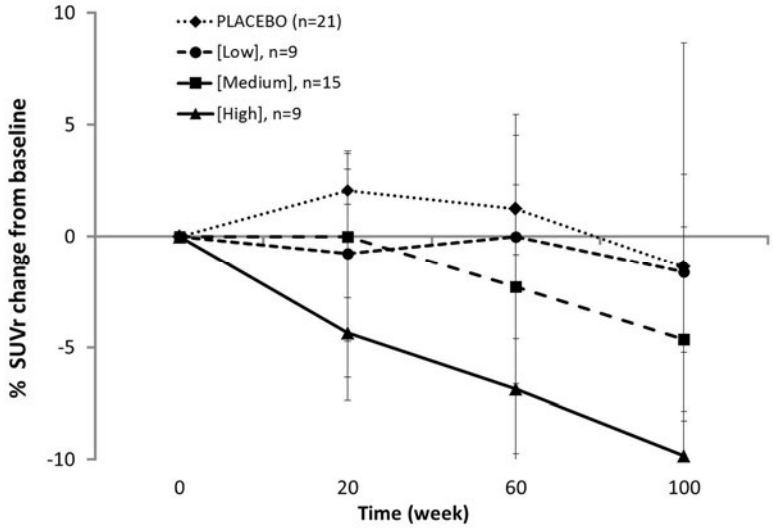
Figure 2 Mean Percent Change from Baseline in Composite Amyloid PET SUVr by Cerebellum Gray Reference: Study WN25203, PET Substudy



PET = positron emission tomography; SUVr = standardized uptake value ratio.

In Study WN25203, a concentration-based analysis of the PET results showed a clear response relationship between gantenerumab concentration in plasma and SUVr reduction, with greater mean concentrations resulting in greater amyloid clearance. As depicted in Figure 3, small changes in SUVr were present in the placebo and 1.9–5-μg/mL gantenerumab groups, whereas the higher concentration groups (5–10 μg/mL gantenerumab and 10–20.72 μg/mL gantenerumab) displayed SUVr reductions of up to 5% and 10%, respectively. These analyses indicate that higher doses may produce greater Aβ clearance that may translate into greater clinical effect.

Figure 3 Median Changes over Time in Concentration-Dependent PET SUVr by Gantenerumab Serum Concentration and Cerebellum Gray Reference: Study WN25203, PET Substudy



PET = positron emission tomography; SUVr = standardized uptake value ratio.
Note: low = 1.9–5 μg/mL; medium = 5–10 μg/mL; high = 10–20.7 μg/mL.

In addition, CSF analyses performed in Study WN25203 showed dose-dependent reductions in both CSF tau species (total tau [t-tau] and phosphorylated tau [p-tau]) in patients receiving gantenerumab compared with placebo. No change in CSF $A\beta_{42}$ was present over the 2-year period, as expected, given the mechanism of action of gantenerumab that targets fibrillar over monomeric Aβ.

Overall, these findings indicate the presence of clinical and biological effects of gantenerumab in subjects who had the highest exposure. In overall study population, results from the futility analysis of Study WN25203 indicated that the likelihood of the 225-mg dose of gantenerumab achieving a clinical effect was very low. These findings indicate that higher doses are required to achieve a clinical effect associated with the biological activity indicated by the amyloid and tau biomarker findings in Study WN25203. As a result, the decision was made to convert Studies WN25203 and WN28745 into OLE studies to give all patients the opportunity to receive higher doses of gantenerumab and to assess the safety of higher doses.

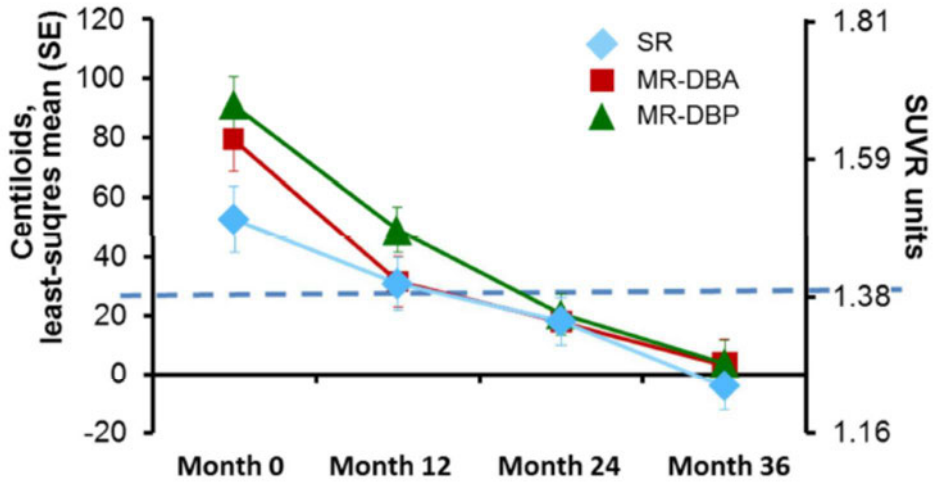
Additional support for using higher doses of gantenerumab comes from PK-PD models. Based on the established similarities between gantenerumab and aducanumab (see Section 1.3), a model characterizing the relationship between plasma drug concentration (PK) and PET response (i.e., the PD effect on amyloid load in the brain) was derived from both gantenerumab Study WN25203 data and aducanumab PRIME data to determine the target dose of gantenerumab for the OLE studies (for further details see

Appendix 4). In the OLE studies, the 1200-mg dose of SC gantenerumab Q4W is predicted to achieve plasma levels comparable to 10 mg/kg of IV aducanumab Q4W and to be associated with a comparable (~20%) amyloid brain reduction, which, in the case of aducanumab, was associated with a statistically significant clinical effect after 1 year of treatment. In order to minimize the occurrence of ARIA-E while achieving the target dose within a reasonable time frame, several titration schedules have been explored in the WN25205 OLE and WN28745 OLE studies.

Gantenerumab PK-PET models of amyloid reduction have been confirmed by PET data from the OLE studies (Klein et al. 2019). There were 89 patients from the OLE studies included in an amyloid PET substudy using [^{18}F] florbetapir (Amyvid™). Of these 89 patients, 67 received follow-up scans at Week 52 of the OLE, 42 received scans at Week 104 of the OLE, and 30 received scans at Week 156 OLE, before the cutoff date of 31 Aug 2019.

Patients were divided into three analysis cohorts because of heterogeneous baseline characteristics, time off-dose before OLE dosing, and OLE titration schedules: 1) MR-DBP (Marguerite RoAD [Study WN28745] double-blind placebo subgroup), which included patients in the placebo arm of Marguerite RoAD (Study WN28745); 2) MR-DBA (Marguerite RoAD double-blind active subgroup), which included patients in the active treatment arms of WN28745; and 3) SR (Scarlet RoAD [Study WN25203] subgroup), which included a combined cohort of all patients from the Scarlet RoAD. SR patients were combined into a single cohort because all patients were off-dose for 16–19 months prior to OLE dosing. Out of 67 patients, 27 were in the MR-DBP, 21 were in the MR-DBA, and 19 were in the SR analysis cohorts. In the OLE PET substudies, a marked and consistent reduction of amyloid load in patients receiving high-dose gantenerumab was observed (see Figure 4). Mean PET centiloid reductions from baseline were –42, –48 , and –21 at Week 52; –71 , –62 , and –36 at Week 104; and –90, –75 , and –57 at Week 156 in the MR-DBP, MR-DBA, and SR analysis cohorts, respectively (see Figure 4). Amyloid reductions are consistently seen in nearly all patients of the three analysed subgroups (see Figure 5 and Figure 6).

Figure 4 Mean (SE) PET Amyloid Reductions in the OLE PET Substudies



Absolute centiloids[a]				
SR	52.7 (11.1) n = 20	30.9 (8.9) n = 19	18.2 (8.1) n = 12	**–4.1 (8.0)** n = 9
MR-DBA	79.6 (10.9) n = 21	31.7 (8.6) n = 21	18.1 (8.2) n = 11	**3.3 (9.0)** n = 6
MR-DBP	91.1 (9.6) n = 27	49.1 (7.6) n = 27	20.6 (6.9) n = 17	**4.0 (7.8)** n = 8

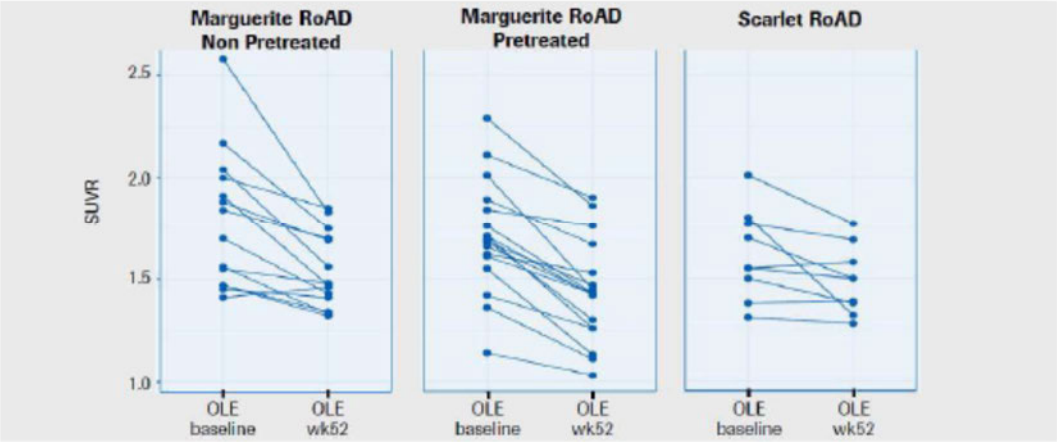
Data presented at Clinical Trials in Alzheimer's Disease (CTAD) Asia in 2019

MR-DBA = Marguerite RoAD (WN28745) pretreated subgroup; MR-DBP = Marguerite RoAD (WN28745) non-pretreated subgroup; OLE = open-label extension; PET = positron emission tomography; SE = standard error; SR = Scarlet RoAD (WN25203) subgroup; SUVR = standardized uptake value ratio.

[a] Analysed using a mixed-model for repeated measures.

The data from the OLE PET substudies showed higher reductions of amyloid plaque over a shorter time period with the 1200-mg dosing regimen of gantenerumab compared with the 105- or 225-mg dosing regimen. Mean amyloid levels were reduced by 39 centiloids by Week 52 and by 59 centiloids by Week 104, a 3.5-times greater reduction than was seen after 2 years at 225 mg.

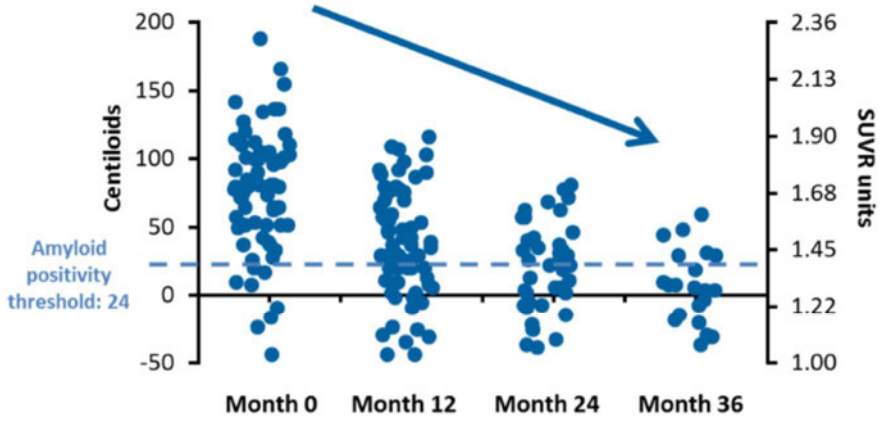
Figure 5 SUVR Reductions during the First Year of High-Dose Gantenerumab Treatment in the OLE PET Substudies



Data presented at CTAD in 2017.
OLE, open-label extension; SUVR, standardized uptake value ratio; wk, week

An important anchor for interpreting PET results is the threshold for amyloid positivity, which is the quantitative threshold that best discriminates pathologically verified absence of plaques or sparse plaques from moderate to frequent plaques. A centiloid value of 24 is generally recognized as the amyloid positivity threshold for florbetapir (Klein et al. 2019). Results in this ongoing study confirm the amyloid plaque removal component of the gantenerumab mechanism of action and show that following two years of treatment, 51% of subjects achieved below-threshold PET SUVr signals based on quantitative measures and that 74% of subjects were below threshold after three years of treatment (see Figure 6).

Figure 6 Patient-Level Amyloid Reductions Over 3 Years of Treatment in the OLE PET Substudies



Proportion of patients below amyloid positivity threshold

No. of patients	68	67	40	23
% below threshold	15%	37%	51%	74%

Data presented at CTAD Asia in 2019
SUVR, standardized uptake value ratio

1.3.2 Rationale for Dosing Strategy

As indicated in Section 1.3.1, the target dose of 1200 mg G3 material administered in the WN25203 and WN28745 OLE studies has been identified based on PK-PD modeling and simulations (details about the model are presented in Appendix 4) and is predicted to lead to an amyloid PET reduction similar to 10 mg/kg IV aducanumab Q4W. The OLE PET data have been consistent with these predictions.

In the OLE Studies WN25203 and WN28745, patients were allocated to different titration schedules (two schedules in Study WN25203 and four schedules in Study WN28745) according to their *APOE* allele status and treatment arm during the double-blind period of the parent studies. These titration schedules were implemented in order to mitigate the risk of ARIA events. An ARIA-E hazard model was first developed on bapineuzemab data (Hutmacher et al. 2013). This model, which includes drug concentrations, time since first dose, and *APOE* ε4 allele status, was applied to the double-blind results in Study WN25203; the model was then tested on publicly available aducanumab data from the PRIME study and were used to predict the incidence of ARIA-E events with a high degree of accuracy, including the observed ARIA-E rate differences across *APOE* ε4 allele groups.

Recently, the ARIA-E hazard model has been updated with observations from the WN25203 and WN28745 OLE trials using higher doses of gantenerumab (see Appendix 5).

Using the validated PK-PET and ARIA-E hazard model, multiple titration options have been simulated, including separate simulations for *APOE* ε4 allele carriers and non-carriers. Two different types of titration schedules, reflecting the different risk for ARIA events between *APOE* ε4 allele carriers and non-carriers were considered. Although an *APOE* ε4 genotype–based titration regimen could permit *APOE* ε4 non-carriers to achieve the target dose more quickly, an option with a single, slower titration schedule for all patients is favored as it provides an overall lower risk for ARIA. Given the chronic and gradually progressive nature of AD, the favored option is a single, slow titration schedule for all patients because it is simpler for clinicians, less prone to error, and does not require *APOE* genotyping before the initiation of treatment.

Thus, based on the information from the WN25203 and WN28745 OLE studies, in which gantenerumab (manufactured with G3 process) up to 1200 mg Q4W was assessed and shown to be safe for APOE ε4 allele carriers and non-carriers, and based on the internally developed PK-PD models, the following dosing regimen for Study WN29922 was selected: 150 mg Q4W for 3 months, then 300 mg Q4W for 3 months, and then 600 mg Q4W for 3 months, followed by 600 mg Q2W until the end of the study. The switch to a Q2W administration schedule allows patients to decrease the number of SC administrations in the abdomen per visit.

The PK-PD models referenced above were developed based on information from the G3 material and were used to establish the initial dosing regimen for this study. As indicated previously, gantenerumab drug substance manufacturing process was optimized from G3 to G4, and a relative bioavailability study (WP40052) assessed the pharmacokinetic difference between the G3 and G4 material in humans.

The results of this relative bioavailability study (WP40052) show that the AUC_{inf} is approximately 1.18 fold and the C_{max} is approximately 1.05 fold higher after administration of G4 compared with G3. As AUC is considered the driver of the treatment effect, the conversion factor of 1.18 from the G3 to G4 material has been based on the AUC_{inf}. The association between microglial-driven removal of aggregated brain amyloid and AUC has been shown in preclinical experiments and clinical studies. In addition, as gantenerumab exhibits linear pharmacokinetics, the AUC_{inf} after single dose reflects the steady state exposure (AUC_{tau}) after multiple doses.

Based on the above rationale and the fact that gantenerumab manufactured with G4 process was safe and well tolerated, the G3 dosing regimen has been converted into the following G4 dosing regimen for the WN29922 study: 120 mg Q4W for 3 months, then 255 mg Q4W for 3 months, and then 510 mg Q4W for 3 months, followed by 510 mg Q2W until the end of the study. This schedule enables titration to target dose within 9 months (see Table 1), with predicted overall ARIA-E rate of approximately 26% based on the current ARIA-E hazard model. The low starting doses and gradual increase in dosing (i.e., slow titration schedule) are expected to reduce the risk of ARIA-E for both

APOE carriers and non-carriers. An MRI scan, confirming the absence of ARIA-E findings, will be required prior to each dose increase.

Table 1 Proposed Dose and Titration Regimen for Phase III Studies

Month	1	2	3	4	5	6	7	8	9	10
Dosing frequency	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W	Q2W
Dose (mg)	120	120	120	255	255	255	510	510	510	510

1.3.3 Risk-Mitigation Measures for ARIA Findings

ARIA is the most significant adverse event reported in therapies against aggregated forms of Aβ. These findings appear to be dose, time, and *APOE* ε4 allele dependent (Piazza and Winblad 2016).

The mechanism underlying the development of ARIA-E and ARIA-H during anti-amyloid treatment is unknown. Because antibodies target removal of Aβ from both the parenchyma and cerebral vasculature, vessels with preexisting amyloid vascular pathology might become transiently more susceptible to leakage of vascular contents. This pathology results in ARIA-E if the leakage consists of proteinaceous fluid and in ARIA-H if the leakage consists of blood products (Sperling et al. 2012).

Thus, an anti-Aβ therapy that effectively maintains vascular β-amyloid clearance would allow vascular remodeling and may, with time, decrease the risk of such extravasation events (Sperling et al. 2012). This is consistent with experience in previous and ongoing studies and with reported data from the long-term extension study of aducanumab treatment (Viglietta et al. 2016).

Previous and ongoing studies with gantenerumab showed that ARIAs are manageable with MRI monitoring and dose intervention algorithms (i.e., temporary study drug interruption or temporary suspension of uptitration) and that these events are mostly asymptomatic. Data from the long-term extension of the PRIME study (aducanumab) suggested also that a titration up to 10 mg/kg (predicted to be comparable to 1200 mg of SC Q4W G3 gantenerumab (or 510 mg of SC Q2W G4 gantenerumab) per the PK-PD model (see Appendix 4) may reduce the incidence of ARIA-E compared with higher fixed dosing (Viglietta et al. 2016).

In Study WN29922, imaging-related criteria are used to exclude patients with clinically important cerebral vascular disease at baseline, as well as ARIA-related lesions. A slow titration schedule will be implemented to reach the target dose, and MRI monitoring will be conducted during the study at regular intervals (see Appendix 1 for the schedule of activities for the uptitration and MRI schedules). An MRI scan documenting the absence of ARIA-E findings will be required prior to each dose increase. If ARIA findings occur, more intense MRI monitoring, dose adjustments, temporary dose holding, or permanent

discontinuation will be implemented according to an ARIA-related dose-adjustment plan, described in Section 5.1.2. Safety findings (including unblinded individual patient and aggregate data) will be reviewed on a regular basis by the iDMC.

1.3.4 Risk to Participants without Alzheimer's Disease Pathology

Owing to the rigorous screening procedures in this study, including measurement of the CSF tau to $A\beta_{42}$ ratio and/or amyloid PET scan, it is anticipated that only participants with AD pathology will be enrolled. In the event that a participant without amyloid pathology is enrolled, no additional risk is expected. However, such participants may still experience side effects related to administration of gantenerumab (e.g., ISRs and development of anti-drug antibodies [ADAs]).

1.3.5 Overall Benefit–Risk Summary

Overall, the benefit–risk assessment of gantenerumab is based on the following:

- Gantenerumab has shown evidence of reducing amyloid plaques (i.e., observed evidence of brain amyloid reduction) and, thus, shows potential benefit in slowing the progression of AD.
- Findings from the WN25203 and aducanumab PRIME studies provide additional support for the hypothesis that anti-amyloid treatment may be associated with a beneficial clinical effect.
- Results from the double-blind portions, as well as from the OLEs of Studies WN25203 and WN28745, showed that ARIA findings are mostly asymptomatic, non-serious, of mild severity, and do not require permanent cessation of treatment. ARIAs are manageable with MRI monitoring and dose intervention algorithms, as detailed in Section 5.1.2.
- No new safety signal has been identified in the data from the ongoing OLE studies with doses of up to 1200 mg Q4W G3 material. These data support the administration of the target dose of 510 mg Q2W G4 material to both ApoE ε4 carriers and non-carriers in the WN29922 study.
- *The benefit risk ratio of conducting the WN29922 study during the pandemic remains unchanged. This is supported by the preclinical and clinical data collected through the development program of gantenerumab where there has been no indication that gantenerumab administration compromised the immune system or made individuals more susceptible to infections.*
  *Thus, there are no data or biological rationale suggesting that G*antenerumab administration could increase the risk of infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or more severe coronavirus disease 2019 (COVID-19) outcomes.
  Participating in study visits at the investigational sites may however increase the risk of exposure to SARS-COV-2, therefore, whenever appropriate, the Sponsor allows the possibility to perform home visits by adequately trained health care professionals. All necessary precautions will be taken to protect the health of the study participants and minimize the risk of exposure. As such the PI, in addition to

all appropriate study staff that come into contact with the study participants, will wear personal protective equipment during the visit as per local requirements.

Thus, the anticipated benefit–risk profile of gantenerumab supports clinical trials with higher doses in the population with early (prodromal to mild) AD.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of gantenerumab compared with placebo in participants with early (prodromal to mild) AD. Specific objectives and corresponding endpoints for the study are outlined in Table 2 for the double-blind treatment period and in Table 3 for the OLE period.

Table 2 Objectives and Corresponding Endpoints for the Double-Blind Treatment Period

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of gantenerumab administered by SC injection compared with placebo	The change from baseline (Day 1) to Week 116 [a] in global outcome, as measured by the CDR-SOB
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo on cognition and function	The change from baseline to Week 116 [a] in cognition and/or function as measured by: • MMSE total score • ADAS-Cog11 and ADAS-Cog13 • Verbal Fluency Task • Coding • FAQ • ADCS-ADL total score and instrumental score
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo	The change from baseline to Week 116 [a], in the following: • Clinically evident decline *as measured using the CDR* • Severity, as assessed by the CDR Global Score • Dependence level, as derived from the ADCS-ADL score • Health-related quality of life, as assessed by the QoL-AD scale • Behavioral and neuropsychiatric symptoms of AD, as measured by the NPI-Q • Study partner burden, as assessed by the ZCI-AD scale • Elements of resource utilization, as assessed by the RUD-Lite • Health outcomes in participant and study partner, as measured by EQ-5D questionnaire

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

[a] If the double-blind treatment period is extended by a total of 24 weeks, the endpoints will be based on change from baseline to Week 128.

Table 2 Objectives and Corresponding Endpoints for the Double-Blind Treatment Period (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of gantenerumab compared with placebo	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Presence of ADAs during the study relative to the presence of ADAs at baseline (in active treatment group only)
Pharmacodynamic Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo in participants with early (prodromal to mild) Alzheimer's disease	• Change from baseline *to Week 116* in brain amyloid load, as measured by amyloid PET scan in a subset of participants • Change from baseline *to Week 116* in brain tau load, as measured by tau PET scan in a subset of participants • Change from baseline *to Week 116* in cerebral spinal fluid markers of disease in a subset of participants, including total tau, and phosphorylated tau
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo in participants with early (prodromal to mild) Alzheimer's disease	• Change over time in plasma *and other CSF* biomarkers (see Section 4.5.6.2) • Change from baseline to Week 116 [a] in functional brain connectivity, as measured by resting-state functional MRI (where available) • Change from baseline to Week 116 [a] in integrity of white matter, as measured by DTI-MRI (where available) • *MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all participants*
Exploratory Pharmacokinetic Objective	***Corresponding Endpoint***
• *To characterize the PK profile of gantenerumab*	• *Plasma concentration of gantenerumab (administered subcutaneously) at specified timepoints*

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

[a] If the double-blind treatment period is extended by 24 weeks, the final endpoints will be based on change from baseline to Week 128.

Table 3 Objectives and Corresponding Endpoints for the Open-Label Extension Period

Safety Objective	Corresponding Endpoints
• To evaluate the long-term safety and tolerability of SC gantenerumab in participants with early AD	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Presence of ADAs during the study relative to the presence of ADAs at baseline
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To assess the long-term efficacy of SC gantenerumab in participants with early AD	• The change in cognition, function and other outcomes over time, as measured by: • CDR • MMSE • ADAS-Cog11 and ADAS-Cog13 • Verbal Fluency Task • Coding • FAQ • ADCS-ADL • Health-related quality of life, as assessed by the QoL-AD scale • Behavioral and neuropsychiatric symptoms of AD, as measured by the NPI-Q • Study partner burden, as assessed by the ZCI-AD scale • Elements of resource utilization, as assessed by the RUD-Lite • Health outcomes in participant and study partner, as measured by EQ-5D questionnaire

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

Table 3 Objectives and Corresponding Endpoints for the Open-Label Extension Period (cont.)

Exploratory Pharmacodynamic Biomarker Objective	Corresponding Endpoints
• To evaluate the long-term effect of SC gantenerumab in participants with early AD	• Brain amyloid load over time, as measured by amyloid PET scan in a subset of participants • Brain tau load over time, as measured by tau PET scan in a subset of participants • Cerebral spinal fluid markers of disease over time in a subset of participants, including, but not limited to, $A\beta_{1-42}$, total tau, and phosphorylated tau • MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, functional brain connectivity, integrity of white matter in all participants • Plasma markers over time *in all participants*

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of gantenerumab in participants with early (prodromal to mild) AD.

The planned number of participants for the global enrollment phase for the study is approximately 1016 participants randomized in a 1:1 ratio to receive gantenerumab and placebo (508 participants randomized to gantenerumab and 508 randomized to placebo) (see Section 6.1). To maintain a balanced number of participants enrolled in each treatment arm and to ensure that the arms are comparable, randomization will be stratified by stage of disease (prodromal AD vs. mild AD), APOE allele status (presence vs. absence of the ε4 allele), use of AD medication (presence vs. absent), geographic region (Western Europe and Australia vs. Rest of the World vs. North America) and participation in longitudinal amyloid and tau PET substudies. Approximately 175 centers in approximately 15 countries worldwide will participate in this study.

Participants will be selected on the basis of clinical diagnosis of probable AD (according to the National Institute on Aging/Alzheimer's Association [NIA/AA] diagnostic criteria and guidelines for AD; see Appendix 2) (McKhann et al. 2011) or prodromal AD (according to the NIA/AA diagnostic criteria and guidelines for MCI due to AD; see Appendix 3) (Albert et al. 2011). The aim of the study is to recruit approximately 50% of the participants with prodromal AD.

Eligible participants will be 50–90 years old, inclusive, must show evidence of β-amyloid pathology as indicated by the CSF tau to Aβ42 ratio (CSF-enrolled participants) or positive amyloid PET scan by visual read (PET-enrolled participants), and meet eligibility criteria as detailed in Section 4.1.

The study will consist of a screening period of up to 12 weeks in length following the signing of informed consent. Sites also have the option to prescreen participants on the FCSRT and MMSE. Participants must sign a separate Informed Consent Form before administration of these tests if used for prescreening. If the results confirm a participant's eligibility, then the FCSRT and MMSE will not have to be completed again during the screening period as long as the test has been done within 12 weeks prior the baseline.

Eligible participants will then undergo baseline visit assessments (Day 1) prior to receiving the first dose of blinded study drug (gantenerumab or placebo). Participants will continue in the double-blind treatment period.

Due to the global impact of the COVID-19 pandemic and the resulting disruption in study drug administration, the duration of the double-blind treatment period will be extended by 12 weeks, with the possibility of an additional 12-week extension (for a total of 24 weeks). This may result in the following scenarios:

- Scenario 1: Participants who are enrolled and active in the double-blind treatment period after implementation of Protocol Version 4 will have the double-blind treatment period extended by 12 weeks, with the final efficacy and safety visit at Week 116 (Appendix 1).
- Scenario 2: If the COVID-19 pandemic results in greater than anticipated disruptions to study drug administration, then the Sponsor has the option to extend the double-blind treatment period by an additional 12 weeks, with the final efficacy and safety visit at Week 128 (Appendix 1). This extension will be mandatory for all patients who are active in the double-blind treatment period at the time that the extension decision is implemented.

Participants who have already had the last study drug administration at Week 102 and their final efficacy and safety visit at Week 104 and who have completed the double-blind treatment period prior to implementation of *the study extension by 12 weeks*, will continue into the OLE of either the WN29922 study or the WN42171 study. Alternatively, they will continue into the safety follow-up period.

For participants who enroll or who are active in the double-blind treatment period at the time of implementation of *the study extension by 12 weeks*, visits and study drug administration will occur Q4W until participants reach the target dose, which will be 510 mg Q2W. After the last dose of study drug (Week 114 for scenario 1 and Week 126 for scenario 2, if applicable), final efficacy and safety assessments will be performed 2 weeks later (at Week 116 for scenario 1 and at Week 128 for scenario 2, if applicable). Participants may then enroll in an OLE study if they are eligible (either in the OLE part of this study or in the WN42171 study) or have safety follow-up visits 14 and 50 weeks after the last dose for safety and limited efficacy assessments.

All participants who prematurely discontinue treatment will continue participating in the study and will be asked to return for collection of safety and limited efficacy data (see Section 4.7.1).

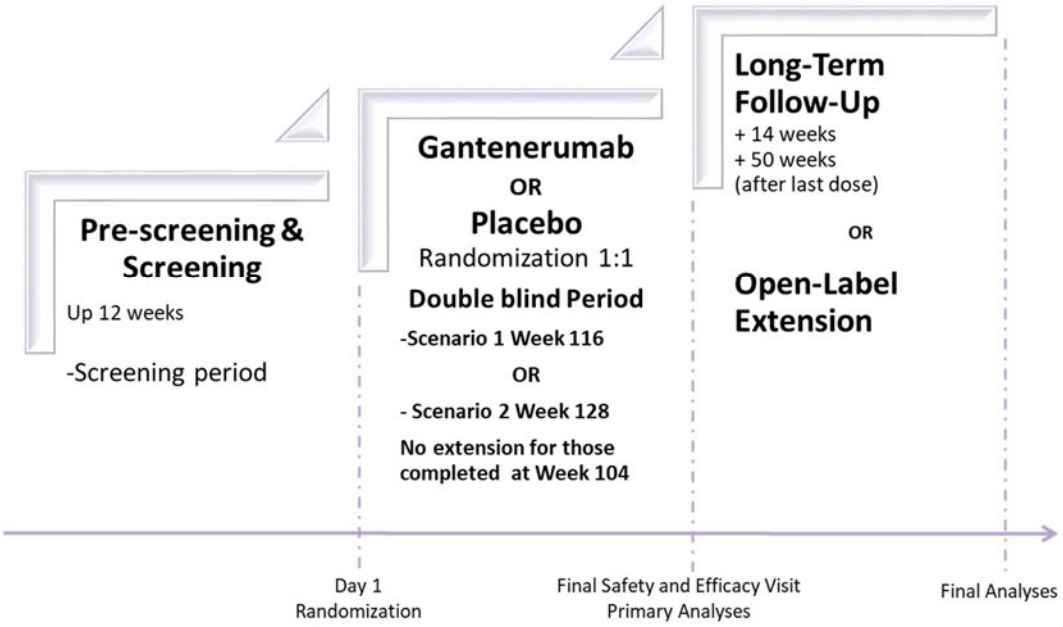
Participants will undergo brain MRI examinations for safety monitoring and longitudinal changes in brain structure. MRI scans will be read by a central MRI reader (for more details regarding imaging-related criteria, see Section 4.1.2.2). Participants will also undergo standard tests to monitor safety (blood tests, ECG), as well as the Columbia–Suicide Severity Rating Scale (C-SSRS) to monitor for suicidality, tests for cognition, function, and QoL status. Blood samples for the assessment of PK samples, PD biomarkers, and ADA will be obtained from all participants.

The incidence and nature of adverse events, serious adverse events, ARIA-E, ARIA-H, ISRs, adverse events of special interest, ECGs, and laboratory abnormalities will be assessed on a regular basis by an unblinded iDMC.

An overview of the study design is provided in Figure 7. The schedule of activities is provided in Appendix 1.

Once the double-blind treatment period is completed, participants who consent and are eligible may opt to participate in an OLE. If the stand-alone open-label study (Study WN42171) is not open for enrollment at the time that a participant completes the double-blind treatment period of this study, then the participant will follow the OLE procedures described in this study (Section 4.3.2.2 and Appendix 1). These participants will then transition to Study WN42171 after they have completed the entire schedule of activities in the OLE of this study and the protocol for Study WN42171 is available and approved as per local requirements. If Study WN42171 is open for enrollment at the time that a participant completes the double-blind treatment period of this study, then the participant will enroll directly in Study WN42171 and not in the OLE portion of this protocol. *The OLE of Study WN29922 is not applicable in countries that cannot run Study WN42171.*

Figure 7 Overall Study Design



W=week

The study consists of three distinct periods:

- Screening (including an optional pre-screening): The screening period may last up to 12 weeks for each eligible participant.
- Double-blind treatment period: After screening, participants who meet all eligibility criteria will be randomly assigned to one of two arms (gantenerumab or placebo) in a 1:1 ratio. Following baseline assessments, each participant will receive a minimum of nine SC Q4W administrations of study drug (uptitration period), followed by up to 40 administrations of study drug in the double-blind treatment period in scenario 1 or up to 46 administrations in scenario 2, if applicable. The last dose of study drug will be administered at Week 114 in scenario 1 and at Week 126 in scenario 2, if applicable. At the end of the double-blind treatment period, 2 weeks after the last dose, all participants will undergo the final safety and efficacy study visit. Participants who have already completed the double-blind treatment period prior to implementation of *the study extension by 12 weeks* will have received 34 SC Q2W administrations of study drug during the double-blind treatment period. The last dose will be administered at Week 102, and their final efficacy and safety visit will be at Week 104.
- Post–double-blind treatment period: After the final efficacy and safety study visit, all participants will be asked to come back for the long-term follow-up visits or to continue in the OLE.

  Long-term follow-up: Long-term follow-up will consist of a 50-week follow-up period with evaluations at Weeks 14 and 50 after completion of study drug

administration. Participants who withdraw early during the double-blind treatment period or during the OLE period are also asked to complete the long-term follow-up visits.

OLE: All eligible participants will have the opportunity to enter an OLE study.

- Eligible participants who enrolled early in the WN29922 study may start the OLE as detailed in Appendix 1, Table 5, and Table 6, and will then transition to the open-label Study WN42171 (details will be provided in Protocol WN42171). Participants who terminated the WN29922 OLE early will be asked to come back for long-term follow-up visits.
- If the WN42171 protocol is available and approved by local authorities, the eligible participants will directly be enrolled in the open-label Study WN42171.

For the schedule of activities at each visit, see Appendix 1.

China Enrollment Plan

Based on historical data, participant recruitment is expected to take longer in China; therefore, a specific China enrollment plan has been established. Thus, if at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA during the global enrollment phase, additional participants may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. All participants enrolled at NMPA-recognized sites in the global enrollment phase will be included in the primary analysis. All participants enrolled at NMPA-recognized sites in the global enrollment phase and the China extension phases will be included in a China-specific analysis. Details will be provided in the SAP.

3.1.2 Substudies

The substudies associated with Study WN29922 will be described in separate protocols, and participants consenting to enroll in these substudies will be asked to sign the associated Informed Consent Forms.

To date, there are two substudies associated with Study WN29922: a longitudinal Amyloid PET substudy and a longitudinal Tau PET substudy. The amyloid- and tau PET assessments will allow a longitudinal evaluation of the effect of gantenerumab on brain amyloid deposition as measured by florbetaben or flutemetamol PET radioligands and tau burden as measured by [^{18}F] GTP1 (an investigational radioligand for in vivo imaging of tau protein aggregates) in participants with early AD. Details of any interim analyses relating to the substudies will *also* be described in the substudy protocols.

The PET data that are collected are expected to help in understanding the effects of gantenerumab on amyloid and tau pathology over time as well as the relationship between change in florbetaben/flutemetamol/[^{18}F] GTP1-PET and changes in other endpoints in the Study WN29922.

3.1.3 Data Monitoring Committee

The iDMC will evaluate participant safety and efficacy on a regular basis. In addition to the data defined in the iDMC Charter (e.g., the incidence and nature of adverse events, serious adverse events, adverse events of special interest, ARIA-E, ARIA-H, and ISRs), the iDMC will review all necessary cumulative data at regular intervals during the study, including efficacy when needed. It is anticipated that these assessments will occur approximately every 3 months. At the time of each review, the iDMC will make appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, the treatment regimen should be modified, the protocol should be amended, enrollment should be held pending further safety evaluations). The iDMC will also evaluate planned or unplanned interim analyses for efficacy or futility (see Section 6.7.1).

Decisions will be made in consideration of the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities are detailed in the iDMC Charter.

Final decisions will rest with the Sponsor.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for safety analyses or safety follow-up is received for the last participant, whichever occurs later.

The study will consist of a screening period of up to 12 weeks (including the optional prescreening period) for each eligible participant who signs the Informed Consent Form and agrees to participate, followed by a double-blind treatment period of study drug treatment plus a visit 2 weeks after the last dose. The duration of the double-blind treatment period is extended by 12 weeks (116 weeks in total in scenario 1). In case scenario 2 is implemented, the double-blind treatment period will be extended by 24 weeks (128 weeks in total in scenario 2, if applicable). For participants not entering the OLE period, this will be followed by the post–double-blind treatment period of two follow-up visits at 14 and 50 weeks after the last dose. Thus, for a participant not entering the OLE period, the maximum length of study is approximately 176 weeks in scenario 1 or 188 weeks in scenario 2 (if applicable).

For participants entering the OLE period, the extension will consist of an open-label period of at least 35 weeks. If a participant is ready to be uptitrated to the target dose and if the safety MRI allows, the participant will then be transitioned to the WN42171 open-label study. If there is an ongoing ARIA-E, the participant will remain in Study WN29922 until the ARIA-E resolves and the participant is ready to be uptitrated to the target dose. In case the dosing is temporarily interrupted for any other reason, the

participant will be kept in the WN29922 study until they are ready to be uptitrated to the target dose. Participants who are not willing to transition to the WN42171 open-label study after OLE Week 35 will be asked to come back for two follow-up visits at 14 and 50 weeks after the last dose (OLE Follow Up 1 and Follow Up 2, respectively).

3.3 RATIONALE FOR STUDY DESIGN

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of gantenerumab in participants with early (prodromal to mild) AD, increased amyloid burden (defined according to CSF or PET criteria), and clinical symptoms.

3.3.1 Rationale for Participant Population

As the accumulation of Aβ brain amyloid begins before the onset of AD dementia, it is reasonable to postulate that the benefit of anti-amyloid therapy may be greater if initiated at an early stage of the disease. For this reason, Roche has focused clinical development of gantenerumab on early (prodromal to mild) AD.

Participants in this study are required to meet standard research criteria for mild AD (according to the NIA/AA research criteria and guidelines for AD; see Appendix 2) or prodromal AD (according to the NIA/AA research criteria and guidelines for MCI due to AD; see Appendix 3). Note that the terms “prodromal AD” and “MCI due to AD” are considered to refer to the same population in this study and are defined according to NIA/AA research criteria and guidelines for MCI due to AD. Thus, participants with prodromal AD will present with documented objective evidence of deficit in one cognitive domain. Participants with mild AD must present with documented deficits in at least two cognitive domains and evidence of functional decline. Overall, the population will have an MMSE between 22 and 30 (inclusive) points and a CDR global score (CDR-GS) of 0.5 or 1.0. The MMSE score provides evidence of no more than mild disease severity and the CDR-GS score indicates that the participants have prodromal AD or cognitive and functional deficits consistent with mild AD. The aim of the study is to recruit approximately 50% of the participants with prodromal AD.

Gantenerumab is an antibody that targets Aβ. Thus, the study population should have documented evidence of amyloid pathology. This participant selection approach is consistent with the NIA/AA research diagnostic criteria and guidelines for AD as well as with the Qualification Opinion from the European Medicines Agency’s (EMA’s) Committee for Medicinal Products for Human Use on the use of CSF biomarkers for enrichment of trials in mild to moderate AD dementia (2012), and the U.S. Food and Drug Administration (FDA’s) draft guidance for early AD (2013). Although the FDA’s guidance refers to the early stage of AD in which individuals present with clinical MCI, biomarkers of amyloid pathology are expected to add value to participant selection in mild AD studies, especially for anti-amyloid treatments (McKhann et al. 2011; Dubois et al. 2014, 2016). Biomarker enrichment is important for anti-amyloid therapy

clinical trials because some results of early trials have demonstrated that approximately 20% participants who are enrolled in trials based on a clinical diagnosis of AD alone may not have underlying amyloid pathology as assessed by amyloid PET (Doody et al. 2014; Salloway et al. 2014).

For enrollment in this study, biomarker evidence of β-amyloid deposition will be assessed either by a centralized visual assessment of PET amyloid imaging, using one of the three following amyloid PET imaging tracers (Vizamyl™, Neuraceq™, and Amyvid™ according to country and site availability) or by the CSF tau to $A\beta_{42}$ ratio (using a prespecified cutoff and the Roche Diagnostics Elecsys immunoassay).

Both methods (CSF and PET) are established approaches to identify Aβ accumulation in the brain in vivo (Pannee et al. 2016; Vos et al. 2016) and both have been used in research and in clinical practice. There is also emerging evidence that indicates consistency between PET amyloid imaging and CSF biomarkers. Indeed, in biomarker research studies, concordance between amyloid PET and the combination of CSF $A\beta_{1-42}$ with t-tau has been shown to be very high with properly controlled CSF methodologies (EMA 2012).

To enrich for participants who are more likely to decline over the 2-year trial, all participants have to demonstrate amnestic deficits as measured by the FCSRT's total free recall score and cueing index (Sarazin et al. 2007). The use of the FCSRT to support a hippocampal-related memory deficit (Buschke 1984; Grober and Buschke 1987) has been recommended by the International Working Group (IWG-1; Dubois et al. 2007, 2010). Indeed, the core clinical symptom of AD is significant and progressive episodic memory impairment. Memory impairments because of AD are known to be hippocampal dependent and are thought to be characterized by a deficit in recall, which is often not recovered with cueing.

The FCSRT is a cued recall test that uses controlled encoding to ensure that impaired recall and cueing results are due to memory impairment and are not a failure at encoding (e.g., by means of attentional impairment). The FCSRT has demonstrated high sensitivity and specificity in differentiating participants with AD from both healthy controls and participants with other forms of dementia (Grober et al. 2008, 2010). More recently, the choice of the FCSRT as a valid clinical marker for typical prodromal AD (amnestic MCI) has been endorsed by the IWG-2 (Dubois et al. 2014) and is supported by studies showing that this test is a good tool to use for predicting progression to AD for participants with prodromal AD (Mura et al. 2014; Lemos et al. 2015). In addition, data generated from Roche datasets showed that a cueing index of ≤ 0.67 is a good predictor of cognitive decline. Therefore, the FCSRT cueing index of ≤ 0.67 and a free recall score of ≤ 27 have been selected as inclusion criteria for this study. The cueing index measures the ability of a participant to benefit from being reminded using specific cue words to recall the target word. To prevent participants who have a high free recall and who do not appear to benefit from being reminded from being included simply because

of apparent low cueing index, a free recall score of ≤27 will also be required. The FCSRT index is consistent with that published by Sarazin et al. (2007) and Auriacombe et al. (2010).

3.3.2 Rationale for Use of a Placebo Control Group

Study WN29922 is a placebo-controlled trial in which participants will be eligible for study participation whether or not participants are receiving standard-of-care medications for AD (i.e., acetylcholinesterase inhibitors, memantine, and/or medical food supplements). Given that there are currently no approved disease-modifying compounds that could serve as an active control, participants will be randomized to receive gantenerumab or placebo on top of background therapies.

3.3.3 Rationale for Gantenerumab Dosage and Titration Schedule

In the OLE studies (WN28745 and WN25203), different titration schedules (based on prior double-blind treatment exposure and *APOE* ε4 status) have been utilized to enable all participants to reach a target dose of 1200 mg SC Q4W while managing the risk for ARIA with MRI monitoring and dose intervention algorithms. In addition, data from the OLE studies support treatment at a low starting dose with a gradual increase in dosing (i.e., slow titration schedule) to reach target dose and to reduce the risk of ARIA findings.

As presented in Section 1.3.2, a target dose of 510 mg Q2W along with a titration schedule with a low starting dose and gradual increase in dosing (i.e., slow titration schedule) that is expected to reduce the risk of ARIA-E for both APOE carriers and non-carriers have been identified for the current study.

Therefore, all participants in Study WN29922 (regardless of APOE ε4 status) will receive 120 mg of SC gantenerumab Q4W for 3 months, 255 mg SC Q4W for 3 months, and 510 mg SC Q4W for 3 months prior to reaching target dose of 510 mg Q2W after 9 months of titration (see Section 1.3.2 for additional details about the conversion of G3 dosing regimen to G4 dosing regimen). Based on the model predictions (see Appendix 5), the overall ARIA-E rate is expected to be approximately 26%. An MRI scan, confirming the absence of ARIA-E findings, will be required prior to each dose increase.

3.3.4 Rationale for Treatment Duration

3.3.4.1 Rationale for Double-Blind Treatment Duration

According to the EMA's guidance on medicinal products for the treatment of AD and other dementias (EMA 2018) controlled clinical trials aimed at demonstrating short-term improvement in mild to moderate AD should last at least 6 months. In order to establish an effect on disease progression, a distinction between symptomatic and disease-modifying effects of a medicinal product has to be made. In addition to demonstrating a relationship between clinical outcomes and an effect on biomarkers of disease pathology, clinical improvement must be shown over a time period that is relevant to the proposed mechanism of action and the expected natural progression rate

of the disease. In AD research, long-term placebo-controlled trials are needed in order to allow time for an efficacious therapy to reverse a longstanding disease process as well as to allow time for a sufficient number of placebo-treated participants to progress. Eighteen months was assumed to be of sufficient length in some recently completed Phase III studies of anti-Aβ antibodies (EMA 2018). In prodromal disease stages, even longer studies may be necessary. In addition, placebo decline is expected to be greater in longer studies; this greater decline allows an increased potential to demonstrate a treatment effect.

A 2-year treatment duration was selected as the most appropriate duration for assessment of the primary endpoint. The duration was based on the mechanism of action of gantenerumab, which is expected to delay and reduce AD progression over time compared with control. As 9-month titration period to reach the target dose is needed, a 2-year treatment period may also be appropriate for the assessment of the primary endpoint. To capture an earlier signal of efficacy, should it be present, assessments relevant to the study objectives will also be obtained at 6, 12, and 18 months.

Measures taken globally during the COVID-19 pandemic are expected to affect the protocol-specified administration of study drug. At the date of writing Protocol Version 4, it is expected that participants will miss an average of 8 weeks of study drug administration over the course of the original 2-year study. This has the potential to decrease the power of the study (see Section 6.1 for details). To mitigate the impact of missed administrations, the double-blind treatment period is being extended by 12 weeks. The continuing impact of the COVID-19 pandemic on study procedures will be closely monitored. If the COVID-19 pandemic results in greater than anticipated disruptions to study drug administration, the Sponsor may further extend the double-blind treatment period by an additional 12 weeks (24 weeks in total).

3.3.4.2 Rationale for OLE Treatment Duration

An open-label treatment duration of at least 9 months has been selected to offer the first participants randomized in Study WN29922 open-label gantenerumab until the Protocol WN42171 open-label study is available and approved. A duration of 9 months corresponds to the uptitration period; thus, when these first participants reach the target dose, they will be able to start the WN42171 open-label study at the target dose (i.e. 510 mg Q2W).

3.3.5 Rationale for Long-Term Follow-Up

The primary objective of the long-term follow-up is to estimate the long-term safety of gantenerumab over an extended period of time. Study assessments performed 14 and 50 weeks after the last dose of study drug will be used to evaluate the effects of treatment on both efficacy and safety parameters over an extended period after study drug discontinuation. Assessments will be conducted for all participants who discontinue treatment during the double-blind treatment period, during the OLE period, or who complete the double-blind period but do not enter the OLE period or who complete the OLE period but do not enter in the WN42171 open-label study. Assessments will also allow for the exploration of the long-term effects with declining drug exposure.

3.3.5.1 Rationale for Duration of Study Follow-Up (14 Weeks)

The primary purpose of the 14-week follow-up visit (i.e., 14 weeks after the last dose) is to evaluate the long-term safety of gantenerumab. The apparent terminal half-life of gantenerumab is in the order of 24 days, and gantenerumab is cleared from plasma after approximately 16 weeks (approximately 5 half-lives). Therefore, safety assessments performed 14 weeks after the last dose are considered sufficient to evaluate residual effects on peripheral safety outcomes. In addition, efficacy assessments at the follow-up visit may support an enduring effect of gantenerumab after treatment is stopped.

3.3.5.2 Rationale for Long-Term Follow-Up (50 Weeks)

Assessments performed 50 weeks after the last dose will be used to evaluate the long-term effects of study drug on both efficacy and safety parameters. The assessments will allow for the exploration of the long-term effects of study drug given the expected level of decline over this period. Participants will not be restricted from starting new treatment and therefore, the analysis will be considered exploratory.

3.3.6 Rationale for Primary Outcome Measure: Clinical Dementia Rating–Sum of Boxes

AD is considered a continuous disease that passes through consecutive stages without discrete transition points. Thus, the use of a single endpoint across both subpopulations of early (prodromal to mild) AD is consistent with the current understanding of AD.

Showing the benefit of new therapies for participants in the early stages of AD is challenging, owing to the lack of sensitive assessment tools. Use of the CDR-SOB as the primary outcome measure for studies of early (prodromal to mild) AD enables simultaneous demonstration of benefit on primary symptoms and clinical relevance (Aisen 2009, 2011), while also ensuring use of a clinical outcome assessment with adequate measurement properties (FDA 2013).

The Washington University CDR is a global assessment instrument that yields global scores (GS) and SOB scores. The CDR is derived from a semi-structured interview with the participant and an appropriate informant, and it rates impairment in six categories (memory, orientation, judgment and problem solving, community affairs, home and

hobbies, and personal care) on a 5-point scale for which 0 = no impairment, 0.5 = questionable impairment, and 1, 2, and 3 = mild, moderate, and severe impairment, respectively. From the six individual category ratings, or box scores, the CDR-GS is established by clinical scoring rules, for which CDR 0 = no dementia and CDR 0.5, 1, 2, or 3 = questionable, mild, moderate, or severe dementia, respectively (Morris 1993). The CDR-SOB score is a detailed quantitative general index that provides more information than the CDR-GS in participants with early (prodromal to mild) dementia (Coley et al. 2011; Cedarbaum et al. 2013). In particular, the CDR-SOB has been proposed for use in longitudinal assessment of dementia and is widely used in AD studies as a global measure of disease progression (Williams et al. 2013). The FDA's draft guidance for developing drugs for the early stages of disease suggests that a composite scale, validated in participants with early-stage disease that includes both cognition and function as a single primary efficacy outcome measure, is appropriate. The CDR-SOB is an example of a measure that fulfills these criteria (FDA 2013) and is now being utilized as the sole primary endpoint in several studies utilizing participant populations with early (prodromal to mild) AD, including the CREAD (crenezumab), PRIME (aducanumab), ENGAGE/EMERGE (aducanumab), and Clarity AD (BAN2401) studies.

3.3.7 Rationale for Pharmacokinetic Sampling

A sparse sampling schedule is being utilized to minimize participant burden and yet provide an adequate characterization of the population PK profile of gantenerumab. The PK data may be combined with available data from other gantenerumab studies and may be used to assess exposure–response relationships for relevant imaging, CSF, plasma PD biomarkers, ECGs, and efficacy and safety outcomes in participants with early (prodromal to mild) AD, as appropriate.

3.3.8 Rationale for Biomarker Assessments

The following biomarker assessments described in Sections 3.3.8.1 (CSF), 3.3.8.2 (PET imaging), and 3.3.8.3 (brain volumetry, connectivity, and fiber tract integrity) will be used to investigate the effect of gantenerumab on the underlying pathology of AD in the participant population.

3.3.8.1 Cerebral Spinal Fluid Biomarkers

Amyloid plaque deposition, neurofibrillary tangle formation, and neuronal degeneration are known pathologic features of AD. Decreased CSF $A\beta_{1-42}$ and elevated CSF t-tau and p-tau are considered a biochemical signature of AD. Accumulating evidence suggests that low CSF $A\beta_{1-42}$ reflects underlying amyloid plaque pathology, whereas increased t-tau and p-tau levels may be reflective of neurodegeneration and/or tau pathology. Amyloid deposition may be the initiating event in the cascade of pathologic processes underlying AD, whereas tau pathology appears to be a subsequent event, and more associated with neurodegeneration. Therefore, t-tau and p-tau may be studied as downstream biomarkers of the primary target of anti-amyloid therapies such as gantenerumab.

Although biomarkers indicative of certain neuropathologies are not surrogate markers for efficacy, there is some evidence that anti-Aβ treatments may cause changes in these biomarkers. A neuropathologic study of participants with AD from Study AN1792 suggests that active amyloid immunotherapy ameliorates neurite abnormalities and tau pathology through decreased tau phosphorylation (Serrano-Pozo et al. 2010). In a pooled analysis of CSF data from two Phase II trials with bapineuzumab in participants with mild to moderate AD, a decrease in both p-tau and t-tau levels relative to baseline was observed in the bapineuzumab group after 12 months of therapy (Blennow et al. 2010). These findings were confirmed in two Phase III studies with bapineuzumab (Sperling et al. 2012) as well as in Study WN25203 with gantenerumab. In Study WN23203, CSF biomarkers were analysed for changes in multiple proteins, including $A\beta_{1-42}$, t-tau, p-tau, and neurogranin, over the 2-year period. Markers of neurodegeneration were significantly reduced in the 225-mg gantenerumab group compared with placebo over 2 years, with greater relative reduction in p-tau relative to t-tau. The greatest effect was reduction in p-tau in the 225-mg gantenerumab arm at 2 years relative to the change in the placebo arm. There was no treatment effect on CSF $A\beta_{1-42}$ (Nikolcheva et al. 2015). Because no evidence of efficacy was demonstrated with these therapies in clinical trials yet, changes in these biomarkers provide meaningful information about the pharmacodynamic effects of gantenerumab and the effect on pathologic processes underlying AD.

Based on these data and on the proposed mechanism of action of gantenerumab, levels of CSF t-tau and p-tau and additional exploratory biomarkers reflecting neurodegeneration will be assessed at baseline and following treatment. Because gantenerumab is expected to clear amyloid from the brain, levels of CSF $A\beta_{1-42}$ will also be measured.

3.3.8.2 Positron Emission Tomography

The definitive diagnosis of AD requires the presence of progressive dementia during life and the postmortem presence of neuropathological lesions (i.e., neuritic plaques composed of β-amyloid aggregates and neurofibrillary tangles formed from hyperphosphorylated tau protein). However, imaging approaches using ligands that demonstrate high affinity for aggregated amyloid are able to provide an assessment of deposition in vivo, which can be evaluated over time (Clark et al. 2011).

3.3.8.3 Brain Volumetry, Connectivity, and Fiber Tract Integrity

A characteristic feature of AD is neuronal destruction. Such neuronal loss is demonstrated at a macroscopic level by progressive cerebral atrophy, which can be tracked on MRI (Fox and Kennedy 2009). Multiple changes in brain anatomy beyond those associated with normal aging have been reported in participants with AD (e.g., enlarged ventricles, decreased cortical thickness, decreased total brain volume, and hippocampal atrophy), and there is evidence for strong correlations between these imaging biomarkers and functional cognitive measures (Li and Wahlund 2011). Based on volumetric MRI measurements, the two most established markers of disease

progression in longitudinal observational studies are hippocampal and whole brain atrophy (Fox et al. 2000, 2005; Jack et al. 2010), with ventricular expansion a related quantitative marker.

Therefore, to quantify the effects of gantenerumab on neurodegeneration, whole brain volume, ventricular enlargement, and regional brain volume changes will be assessed at screening and following treatment. All MRI reads and volume measures will be conducted by the central reader.

In addition to the structural brain volume changes, changes in brain functioning of participants will be assessed using a blood oxygenation level-dependent (BOLD) resting-state functional MRI (rs-fMRI) procedure (at sites where this procedure is available) with a paradigm-free procedure (Grecius et al. 2004; Filippi and Agosta 2011). Increased concentrations of Aβ in the brains of participants with AD contribute to neuronal degeneration in the brain over time and have been associated with reduced functional connectivity of various brain networks using rs-fMRI (Sheline et al. 2010; Binnewijzend et al. 2012; Brier et al. 2012; Sheline and Raichle 2013). Resting-state functional connectivity has been found to be decreased in brain regions such as the hippocampus, the default mode network (regions such as precuneus, anterior cingulate, and parietal and temporal cortices), and cortical regions in which the functional connectivity is continuously decreased as disease progresses. It has also been found to be decreased in cognitively normal elderly participants with brain amyloid deposition (PiB+PET scans). Alteration of the decreased brain functional connectivity has been shown using therapeutic interventions such as memantine (Lorenzi et al. 2011) or donepezil in participants with AD (Goveas et al. 2011; Solé-Padullés et al. 2013). Increased brain functional connectivity was found already after 3 months of treatment with donepezil, which correlated with changes in cognitive measures such as the ADAS-Cog (Goveas et al. 2011; Solé-Padullés et al. 2013). Therefore, therapeutic interventions, which act to remove Aβ from the brains of participants with AD, may help to reverse the altered functional connectivity presumably caused by the accumulation of Aβ in the brain.

The integrity of white matter tracts will be assessed prior to and after treatment with gantenerumab using diffuse tensor imaging (DTI)-MRI techniques. DTI-MRI is based on the measurement of diffusion properties of water molecules in the axonal fiber tracts in white matter. Whereas water molecules can diffuse isotropically in CSF, they are restricted axially in white matter bundles. Widespread group differences in the degree of anisotropic diffusion, or fractional anisotropy (FA), has been seen between participants with AD and healthy subjects (Jack et al. 2015). Greater FA values are thought to indicate greater white matter integrity. Likewise, mean diffusivity, which measures the average rate of diffusion in all directions, has been shown to be higher in AD groups compared with healthy controls, presumably owing to increased white matter injury in participants with AD (Nir et al. 2013).

At sites having the required software and hardware, rs-fMRI (BOLD rs-fMRI) and DTI-MRI will be performed when feasible during the same scanning session as the structural MRI to assess functional brain connectivity and fiber tract integrity before and after treatment with gantenerumab.

4. MATERIALS AND METHODS

4.1 PARTICIPANTS WITH ALZHEIMER'S DISEASE

This study will enroll approximately 1016 participants with increased brain amyloid burden (defined according to CSF or PET criteria), objective memory impairment indicated by cognitive assessment, and a diagnosis of probable AD or prodromal AD based on relevant NIA/AA criteria during the global enrollment phase. Additional criteria are defined in Sections 4.1.1 and 4.1.2.

An increase in sample size may be considered in the event of changes to the sample size assumptions on the basis of blinded data review or factors external to the study.

If at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA during the global enrollment phase, additional participants may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. All participants enrolled at NMPA-recognized sites in the global enrollment phase will be included in the primary analysis. All participants enrolled at NMPA-recognized sites in the global enrollment phase and the China extension phases will be included in a China-specific analysis. Details will be provided in the SAP.

4.1.1 Inclusion Criteria

Participants must meet the following criteria for study entry:

- Ability to provide written consent signed by the participant (co-signed by the participant's legally authorized representative, if required by the local regulations, guidelines, and independent Ethics Committee [EC] or Institutional Review Board [IRB])
- Age 50–90 years old at screening, inclusive
- Availability of a person (referred to as the "study partner" throughout this protocol) who:
  - Agrees to participate throughout the duration of study
  - In the investigator's judgment, has frequent and sufficient contact (e.g., 5 times per week or approximately 10 hours per week) with the participant
  - In the investigator's judgment, is able to provide accurate information regarding the participant's cognitive and functional abilities, including knowledge about domestic activities, hobbies, routines, social skills, and basic activities of daily life; work and educational history; cognitive performance including memory abilities, language abilities, temporal and spatial orientation, judgment and

problem solving; emotional and psychological state; and can report any changes in the general health status

- Agrees to provide information and to complete all aspects of the study at clinic visits (which require partner input for scale completion)
- Signs the necessary Informed Consent Form(s), and has sufficient cognitive capacity to accurately report on the participant's behavior as well as cognitive and functional abilities
- Is fluent in the language used at the site and has sufficiently good general health to have a high likelihood of maintaining the same level of interaction with the participant and participation in study procedures throughout the duration of the study

Every effort should be made to have same study partner participate throughout the duration of the study.

- Fluency in the language of the tests used at the study site
- Willingness and ability to complete all aspects of the study (including MRI, lumbar puncture [if applicable], clinical genotyping, and PET imaging [if applicable])

The participant should be capable of completing assessments either alone or with the help of the study partner.

- Adequate visual and auditory acuity, in the investigator's judgment, sufficient to perform the neuropsychological testing (eye glasses and hearing aids are permitted)
- Evidence of AD pathological process, as confirmed by CSF tau/$A\beta_{42}$ or on amyloid PET scan by qualitative read by the core/central PET laboratory
- Demonstrated abnormal memory function at screening (FCSRT cueing index ≤ 0.67 and free recall ≤ 27)
- Screening MMSE score ≥ 22 and CDR-GS of 0.5 or 1.0
- Probable AD dementia (consistent with NIA/AA core clinical criteria for probable AD dementia) (McKhann et al. 2011) or prodromal AD (consistent with the NIA/AA diagnostic criteria and guidelines for mild cognitive decline due to AD) (Albert et al. 2011)
- If the participant is receiving symptomatic AD medications, a stable dosing regimen for at least 3 months prior to screening and until randomization

Participants receiving GV-971 or who are planning to take GV-971 during the study are not eligible

- Agreement not to donate blood or blood products for transfusion for the duration of the study and for 1 year after final dose of study drug
- Agreement not to participate in other research studies for the duration of this trial and its associated substudies
- For enrollment in the China extension, participants must have residence in mainland China, Hong Kong, or Taiwan and be of Chinese ancestry

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 16 weeks after the last dose of study drug

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

4.1.2.1 Exclusions Related to Central Nervous System Disorders

Participants who meet any of the following criteria related to CNS disorders will be excluded from study entry:

- Any evidence of a condition other than AD that may affect cognition, including, but not limited to, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, Parkinson disease, corticobasal syndrome, Creutzfeldt-Jakob disease, progressive supranuclear palsy, frontotemporal lobar degeneration, Huntington disease, normal pressure hydrocephalus, seizure disorder, delirium or hypoxia
- History or presence of clinically evident systemic vascular disease (e.g., clinically significant carotid/vertebral artery stenosis or plaque, aortic aneurysm), that in the opinion of the investigator has the potential to affect cognitive function
- History or presence of clinically evident cerebrovascular disease (e.g., intracranial or cerebral vascular malformations, aneurysm, intracranial macrohemorrhage)

  Participants with asymptomatic developmental venous anomalies may be eligible after discussion with and approval by the Medical Monitor.
- History or presence of posterior reversible encephalopathy syndrome
- History or presence of any stroke with clinical symptoms within the past 12 months, or documented history within the last 6 months of an acute event that is consistent, in the opinion of the investigator, with a transient ischemic attack
- History of severe, clinically significant (persistent neurologic deficit or structural brain damage) CNS trauma (e.g., cerebral contusion)
- History or presence of intracranial mass (e.g., glioma, meningioma) that could potentially impair cognition

- Presence of infections that affect brain function or history of infections that resulted in neurologic sequelae (e.g., HIV, syphilis, neuroborreliosis, and viral or bacterial meningitis and encephalitis)
- History or presence of systemic autoimmune disorders that potentially cause progressive neurologic disease with associated cognitive deficits (e.g., multiple sclerosis, lupus erythematosus, anti−phospholipid antibody syndrome, and Behçet disease)
- History of schizophrenia, schizoaffective disorder, major depression, or bipolar disorder

  History of major depression is acceptable if participant has had no episode within the past year or is considered in remission or depression is controlled by treatment.
- At risk for suicide in the opinion of the investigator
- Alcohol and/or substance abuse or dependence (according to the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, Version 5) within the past 2 years

  Nicotine use is allowed.

  Marijuana use is not allowed and must be discontinued at least 3 months before screening.

4.1.2.2 Imaging-Related Criteria

Participants who meet any of the following imaging criteria will be excluded from study entry:

- According to the MRI central reader, MRI evidence of any of the following:
  - >2 lacunar infarcts
  - Any territorial infarct >1 cm^3
  - Any white matter lesion that corresponds to an overall Fazekas score of 3 that requires at least one confluent hyperintense lesion on the FLAIR sequence, which is ≥ 20 mm in any dimension
- Combined number of microbleeds and areas of leptomeningeal hemosiderosis (i.e., cumulative ARIA-H) on MRI more than five (and should not include any disseminated leptomeningeal hemosiderosis) based on the review performed by the central reader prior to randomization
- Presence of any other significant cerebral abnormalities, including ARIA-E, as assessed on MRI

- Inability to tolerate MRI procedures or contraindication to MRI, including, but not limited to, presence of pacemakers not compatible with MRI, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan, or any other clinical history or examination finding that, in the judgment of the investigator, would pose a potential hazard in combination with MRI

4.1.2.3 Cardiovascular Disorders

Participants who meet any of the following criteria related to cardiovascular disorders will be excluded from study entry:

- History or presence of clinically symptomatic atrial fibrillation requiring maintenance therapy

  Participants who experienced non-valvular atrial fibrillation that resolved more than 1 year ago and was not associated with prior stroke are eligible.
- Within the last year, unstable or clinically significant cardiovascular disease (e.g., myocardial infarction)

  Heart failure classified as New York Heart Association Class I or II cardiac disease is allowed if not associated with hospitalization within the previous 12 months.
- Uncontrolled hypertension (e.g., blood pressure generally >160 mmHg systolic or >95 mmHg diastolic)

4.1.2.4 Hepatic and Renal Disorders

Participants who meet any of the following criteria related to hepatic and renal disorders will be excluded from study entry:

- Chronic kidney disease, indicated by creatinine clearance <30 mL/min to be calculated by the central laboratory using the Cockcroft-Gault formula at screening, which remains <30 mL/min if retested
- Confirmed and unexplained impaired hepatic function as indicated by screening AST or ALT $\geq 3\times$ the ULN or total bilirubin $\geq 2\times$ ULN

4.1.2.5 Infections and Immune Disorders

Participants who meet any of the following criteria related to infections and immune disorders will be excluded from study entry:

- History of, or known to currently have HIV infection, or hepatitis B or hepatitis C infection that has not been adequately treated in the opinion of the investigator, or history of spirochete infection of the CNS (e.g., syphilis, Lyme disease, or borreliosis)
- Systemically, clinically significantly immunocompromised participants, owing to continuing effects of immune-suppressing medication

4.1.2.6 Metabolic and Endocrine Disorders

Participants who meet any of the following criteria related to metabolic and endocrine disorders will be excluded from study entry:

- Abnormal thyroid function as indicated by abnormal screening tests that are judged to be clinically significant by the investigator, or abnormal thyroid function that requires a new treatment or an adjustment of current treatment

  A participant may be rescreened if there is no improvement in cognition in the investigator's judgment after 3 months of adequate treatment for thyroid function.

- Participants with evidence of folic acid deficiency (as indicated by folic acid level below the lower limit of normal) or vitamin B-12 deficiency (as indicated by vitamin B-12 level below the lower limit of normal and/or methylmalonic acid levels above ULN)

  A participant may be rescreened if there is no improvement in cognition after 3 months of adequate treatment for folic acid or vitamin B-12 deficiency.

- Screening hemoglobin A_{1c} (HbA_{1C}) $>8\%$ (retesting is permitted if slightly elevated) or poorly controlled insulin-dependent diabetes (including hypoglycemic episodes)

  A participant may be rescreened after 3 months to allow optimization of diabetic control.

4.1.2.7 Exclusions Related to Medications

The following medications are prohibited for a pre-specified duration prior to study start, as indicated, and during the entire period of study participation (participants who start these medications during the study may be withdrawn from study treatment):

- Any previous administration of gantenerumab or active immunotherapy (vaccine) that is being evaluated to prevent or postpone cognitive decline
- Any passive immunotherapy (immunoglobulin) or other long–acting biologic agent to prevent or postpone cognitive decline within 1 year of screening
- Any other investigational treatment within 5 half-lives or 4 months prior to screening, whichever is longer
- Any previous administration of GV-971
- Any previous treatment with medications specifically intended to treat Parkinson symptoms or any other neurodegenerative disorder within 1 year of screening and with no plans to initiate such medications prior to randomization

  Certain medications are acceptable if the participant is taking the medicine for a non-neurodegenerative disorder, such as restless leg disorder (e.g., pramipexole).

- Typical antipsychotic or neuroleptic medication within 6 months of screening and with no planned changes prior to randomization except as brief treatment for a non-psychiatric indication (e.g., emesis)

Atypical antipsychotic medications are not allowed except for intermittent short-term use and will need to be discontinued 2 days or at least 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

- Anticoagulation medications within 3 months of screening with no plans to initiate any prior to randomization

  Anti-platelet treatments (e.g., aspirin, clopidogrel, and dipyridamol) are permitted.

  Short-term, perioperative use of anticoagulant medications will not result in permanent discontinuation from the study; however, *for any* such use *it is recommended to* prospectively *seek advice from* the Medical Monitor and temporary study drug interruption *may be required*.

- Chronic use of opiates or opioids (including long-acting opioid medication) within 3 months of screening with no plans to initiate any prior to randomization

  Intermittent short-term use of short–acting opioid medications for pain is permitted except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

- Stimulant medications (amphetamine, methylphenidate preparations, or modafinil) within 1 month of screening and throughout the study
- Chronic use of benzodiazepines, barbiturates, or hypnotics from 3 months before screening and with no plans to initiate any prior to randomization

  Intermittent short-term use of benzodiazepines, buspirone, or short-acting hypnotic medication for sleep or anxiety is allowed except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

4.1.2.8 Other Exclusions

Participants who meet any of the following criteria will be excluded from study entry:

- Other causes of intellectual disability that may account for cognitive deficits observed at screening (e.g., static encephalopathy, closed brain injury, mental retardation)

  This may be based on, for example, the participant's sufficient education or work experience.

- Pregnancy or breastfeeding, or intention of becoming pregnant during the study
- Deformity of the lumbosacral region of the spine that in the opinion of the investigator would contraindicate lumbar puncture in participants who will have lumbar puncture
- Clinically significant abnormal screening blood, CSF (if applicable), or urine results that remain abnormal at retest
- Impaired coagulation (screening prothrombin time [PT] $> 1.2\times$ the ULN that remains abnormal on retest)
- History of cancer, with the following exceptions:
  - If considered to be cured

  - If not being actively treated with anti-cancer therapy or radiotherapy and, in the opinion of the investigator, is not likely to require treatment in the ensuing 5 years
  - For prostate cancer or basal cell carcinoma, no significant progression over the previous 2 years
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins, including gantenerumab
- Hypersensitivity to any of gantenerumab excipients
- Any other severe or unstable medical condition that, in the opinion of the investigator or Sponsor, could be expected to progress, recur, or change to such an extent that it could put the participant at special risk, bias the assessment of the clinical or mental status of the participant to a significant degree, interfere with the participant's ability to complete the study assessments, or would require the equivalent of institutional or hospital care
- Residence in a skilled nursing facility such as a convalescent home or long-term care facility: Participants who subsequently require residence in such facilities during the study may continue in the study and be followed for efficacy and safety, provided that they have a study partner who meets the minimum requirement

4.1.3 Eligibility for the Open-Label Extension

Participants who have been randomized and who have completed the double-blind treatment period will be eligible to participate in the OLE, provided they do not meet any of the following criteria:

- Discontinued from study treatment during the double-blind treatment period.
- Received any other investigational medication during the double-blind treatment period or after the end of double-blind treatment.
- Participation in the OLE deemed inappropriate by the investigator (e.g., any serious medical condition or other concerns that preclude the participant's safe participation in the OLE or ability to comply with the required procedures).
- Presence of ARIA-E findings at the Week *116 (or Week 128, if applicable)* MRI scan (participants who have ongoing ARIA-E findings at the Week *116 [or Week 128, if applicable]* will stay in the double-blind treatment period until the finding is deemed resolved). *For those participants who enroll into the GRADUATE OLE from Week 104, before the double-blind extension took place, eligibility for the OLE would be based on the Week 104 scan.*

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Randomization will be performed centrally using an interactive voice or Web-based response system (IxRS). After screening, participants who meet all eligibility criteria will be randomly assigned to one of two treatment groups (gantenerumab or placebo). The ratio will be 1:1, one active to one placebo. The randomization method will be stratified block-randomization. Randomization to treatment allocation will be stratified by

geographic region (Western Europe and Australia vs. Rest of the World vs. North America), participant *APOE* ε4 status (carrier vs. non-carrier), participant stage of disease (prodromal vs. mild AD), use of AD medication (present vs. absent), and participation in the longitudinal amyloid and tau PET substudies. Except in circumstances in which a health authority, EC, or IRB requires it, a participant will not be told of his or her *APOE* ε4 status. Individual participant *APOE* ε4 genotype results will be blinded to participants, investigators, and the Sponsor. *APOE* ε4 status information will be supplied directly to the IxRS vendor by the central testing laboratory so that the information can be incorporated at the time of randomization. For participants for whom *APOE* ε4 status is already known, the results will be blinded to the Sponsor and as much as possible to the site and central MRI reader.

The study is to be conducted in a double-blind manner to minimize potential bias from investigators and participants. The Sponsor will be blinded to study treatment. Sponsor, participants, and site staff will remain blinded to previous treatment allocation in the OLE period. The Master Randomization or Master Medication List will not be available at the study center, to Roche monitors, Roche project statisticians, or to the project team at Roche. Unblinding should not occur except in the case of emergency situations where knowledge of the study drug assigned would affect participant care. The investigator should make every effort to contact Roche before unblinding a participant. In the event that the investigator unblinds a participant without prior notification, the investigator must contact Roche within 1 working day of the event. Any request from the investigator for information about the treatment administered to study participants for another purpose must be discussed with the Medical Monitor.

If unblinding is necessary for participant management (e.g., in the case of a serious adverse event for which participant management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the investigator wants to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event).

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.2.2) that are considered by the investigator or Sponsor to be related to study drug.

4.3 STUDY TREATMENT

The IMP for this study is gantenerumab.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Gantenerumab and Placebo

Gantenerumab and placebo will be supplied by the Sponsor as liquid formulation ready for SC administration. Packaging of the study drug will be overseen by the Roche Clinical Trial Supplies Department and will bear a label with the identification required by local law, the protocol number, study drug identification, and dose. The packaging and labeling will be in accordance with Roche standard and local regulations. Upon receipt of the investigational products at the site, site personnel should check the product for damage and verify the proper identity, quantity, and integrity of the study drug. Site personnel should report any deviations or product complaints to the monitor upon discovery. For further details, please refer to the Gantenerumab Investigator's Brochure.

For information on the formulation and handling of gantenerumab, see the pharmacy manual and Gantenerumab Investigator's Brochure.

4.3.2 Dosage, Administration, and Compliance

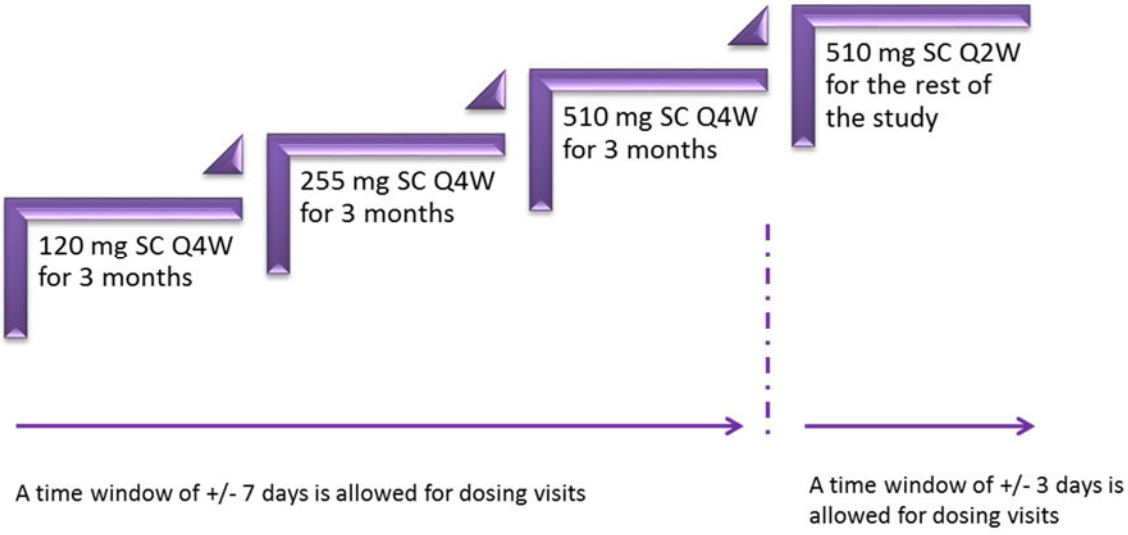
4.3.2.1 Gantenerumab and Placebo Administration during Double-Blind Treatment Period

Gantenerumab or placebo will be administered by SC injection to all participants.

Gantenerumab will be administered by SC injection to all participants randomized to the active treatment arm, regardless of *APOE* ε4 status, at a dose of 120 mg SC Q4W for 3 months, 255 mg SC Q4W for 3 months, and 510 mg SC Q4W for 3 months, prior to reaching the target dose (see Figure 8). Once the target dose is reached, study drug will be administered every 2 weeks (Q2W administration of 510 mg SC gantenerumab). The switch to a Q2W administration schedule allows decreasing the number of SC administrations in the abdomen per visit.

Note: A minimum of 3 doses during each dosing step must be administered prior to uptitration.

Figure 8 Overall Gantenerumab Dosing Design in the Double-Blind Treatment Period



Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous.

For Q4W injections, a time window of ±7 days is allowed for dosing visits. For Q4W injections, the recommended minimum time between doses is 3 weeks. The maximum recommended time between doses should not exceed 6 weeks. Once study drug is administered Q2W, the time window for dosing visits is ±3 days. For Q2W injections, the recommendation is not to administer more than 1020 mg (i.e., 2 times 510 mg Q2W) within 28 days. Always return to the initial planned schedule per randomization for subsequent visits.

Regardless of dose, each participant will undergo up to a total of 49 dosing visits in scenario 1 or 55 dosing visits in scenario 2 (if applicable, see Section 3.3.1) in the double-blind treatment period of the study. Participants who have completed the double-blind treatment period at the time of the implementation of *the 12 week study extension*, will have undergone up to 43 dosing visits. Injections will be administered as one 0.8-mL (120-mg dose), one 1.7-mL (255-mg dose), or two 1.7-mL injections (510-mg dose) subcutaneously to the abdomen, respectively.

Placebo of identical composition (except protein) and identical volume to gantenerumab will be administered by SC injection to all participants randomized to placebo at the same frequency and using the same route of administration.

On study drug administration days that include efficacy assessments (see the schedule of activities in Appendix 1), study drug must be administered at the clinical site. Study

personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

At applicable sites, study drug may be administered by a trained nursing professional at the participant's home or another suitable location, if the participant has given written informed consent to participate in home nursing visits.

Rules for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.2.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.2.2 Gantenerumab and Placebo Administration during the Open-Label Extension Period

During the OLE, participants previously randomized to the active treatment arm will continue to be administered the study drug every two weeks (Q2W administration of 510 mg SC gantenerumab). Participants previously randomized to the placebo arm will be required to undergo 9 months of uptitration.

In order to maintain the previous study treatment blinding (Sponsor, site, and participant), all participants will be dosed every two weeks in the OLE as illustrated in Table 4. As in the double-blind treatment period, a safety MRI has to be performed before each uptitration to ensure that the participant can be uptitrated safely to the next dose.

To ensure blinding to previous treatment, gantenerumab and/or placebo will be administered every 2 weeks as one 0.8-mL and two 1.7-mL injections or two 1.7-mL injections subcutaneously to the abdomen. Injections may contain active gantenerumab or placebo to ensure the correct total dose of active gantenerumab at each visit (see Table 4).

Note: As in the double-blind part, a minimum of 3 doses during each dosing step must be administered prior to uptitration. During uptitration in the OLE, a minimum of 3 doses of each dosing step also have to be administered prior to be eligible for uptitration**. In the OLE, a dose is defined as two consecutive dosing visits (one with an even dose number and one with an odd dose number, see Table 4).**

Table 4 Overall Gantenerumab Dosing Design in the Open-Label Extension

		Open-Label Extension																	
	Visit	Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Wk 26	Wk 28	Wk 30	Wk 32	Wk 34
	Dose Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Participants previously on placebo	Dose	120 mg Q4W						255 mg Q4W						510 mg Q4W					
	Injections (mL)	1× 0.8A + 2× 1.7P	1× 0.8P + 2× 1.7P	1× 0.8A + 2× 1.7P	1× 0.8P + 2× 1.7P	1× 0.8A + 2× 1.7P	1× 0.8P + 2× 1.7P	1× 1.7A + 1× 1.7P	2 × 1.7P	1× 1.7A + 1× 1.7P	2× 1.7P	1× 1.7A + 1× 1.7P	2× 1.7P	2× 1.7A	2× 1.7P	2× 1.7A	2× 1.7P	2× 1.7A	2× 1.7P
Participants previously on active	Dose	510 mg Q2W																	
	Injections (mL)	2× 1.7A + 1× 0.8P	2x 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A

A = Active treatment; Num = number; P = placebo; Wk = week

For the OLE, the time window for dosing visits is ± 3 days. Always return to the initial planned schedule per randomization for subsequent visits.

Rules for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.2.

Participants enrolled in the WN29922 OLE study will have to complete the full titration scheme (i.e., at least 12 weeks on each dosing step) prior to being able to enroll in the WN42171 open-label study where they will receive 510 mg SC Q2W.

On study drug administration days that include efficacy assessments (see the schedule of activities in Appendix 1), study drug must be administered at the clinical site. Study personnel who prepare and administer the study drug must not be involved with any efficacy assessments or safety evaluations.

At applicable sites, study drug may be administered by a trained nursing professional at the participant's home or another suitable location if the participant has given written informed consent to participate in home nursing visits.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

PET Tracers

All participants who are enrolled in PET substudies will be assessed by PET imaging using an appropriate PET ligand. For screening, the possible amyloid PET ligands will be florbetapir, florbetaben, and flutemetamol. According to E.U. guidance, the PET tracers, as used in the context of this study, are designated as non-IMP. In some regions, according to local regulations, these PET tracers may be considered to be IMP.

In countries where the PET radioligands are approved for marketing, the approved local product information will be provided, and in countries where they are not approved for marketing, the Investigator’s Brochures will be provided.

For the safety reporting requirements dealing with the PET tracers used in this study, please refer to Section 5.7).

Details about the PET substudies are described in separate protocols.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (gantenerumab or placebo) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to Gantenerumab

The Sponsor will offer continued access to Sponsor study drug (gantenerumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A participant will be eligible to receive Sponsor study drug (gantenerumab) after completing the study if all of the following conditions are met:

- The participant has a life-threatening or severe medical condition and requires continued Sponsor study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the participant
- The participant and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A participant will not be eligible to receive Sponsor study drug (gantenerumab) after completing the study if any of the following conditions are met:

- The Sponsor study drug is commercially marketed in the participant's country and is reasonably accessible to the participant (e.g., is covered by the participant's insurance or wouldn't otherwise create a financial hardship for the participant)
- The Sponsor has discontinued development of the drug or data suggest that the drug is not effective for AD
- The Sponsor has reasonable safety concerns regarding the drug as treatment for AD
- Provision of the drug is not permitted under the laws and regulations of the participant's country
- Participant is eligible to enroll in an ongoing gantenerumab open-label study

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

All eligible participants will be offered to receive gantenerumab as part of an extension study, as described in Section 3.1.

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a participant from 3 months prior to screening to the study completion or discontinuation visit. All such medications (including name, dose, administration schedule, start and end dates) should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Participants are eligible for study participation whether or not they are receiving approved medication for AD (i.e., acetylcholinesterase inhibitors, memantine, and/or medical food supplements, where approved) with the exception of GV-971. Participants who are receiving GV-971 or who are planning to receive GV-971 during the study are not eligible. Information about background AD medication (e.g., drug name, dose, and start and stop dates, reason for interruption or modification) has to be captured on eCRF. Randomization will be stratified for participants taking and not taking approved anti-dementia medications.

Adding a new medication or changing the dose of a medication after randomization should occur only for the treatment of an adverse event or in case of AD progression. Whenever possible, a medication listed below should be used if appropriate.

The following medications are permitted if the dose and dose regimen have been stable for at least 3 months prior to screening and are expected to remain stable after screening or if required for treatment of an adverse event after randomization:

- Anticonvulsant medications for an approved pain indication
- Selective serotonin reuptake inhibitors for the treatment of depressive symptoms
- Over-the-counter and/or herbal medications, food additive, or any other agent or supplement intended to improve cognition or reduce cognitive decline
- Medications used to treat a mood or anxiety disorder given as maintenance treatment (with the exception of benzodiazepine)
- Intermittent use of short-acting (non-extended release) opioid medications for pain except within 2 days or 5 half-lives (whichever is the longer) of any cognitive assessment (up to a maximum of 3 consecutive days per month)
- Intermittent use of benzodiazepines, including alprazolam, lorazepam, oxazepam, triazolam, or temazepam, or a one-time dose of diazepam or a short–acting hypnotic medication (e.g., zolpidem) if use is intermittent for sleep or anxiety, except within 2 days or 5 half-lives (whichever is the longer) prior to any cognitive assessment
- A dose of benzodiazepine for pre-surgical and pre-imaging sedation at appropriate visits if allowed by the EC or IRB

- Intermittent use of centrally acting antihistamine medications except within 2 days or 5 half-lives (whichever is the longer) prior to any cognitive assessment
- Under certain circumstances, initiation of anti-hemostasis medications during the study conduct

  Anticoagulation therapy lasting no longer than 3 weeks (e.g., temporary usage during surgery) is permitted. Nevertheless, *anticoagulation therapy may require temporary study drug interruption and advice from the Medical Monitor is recommended.*

Concomitant and excluded therapies for determination of participant eligibility are described in Section 4.1.2.7.

Participants who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

4.4.2 Prohibited Therapy

Any medication that is prohibited before screening is also prohibited during conduct of the study (see Section 4.1.2.7). If a participant receives any prohibited treatment during the study, the participant may be withdrawn from study treatment.

4.5 STUDY ASSESSMENTS

Refer to Appendix 1 for the schedule of activities to be performed during the study.

At applicable sites, certain study assessments may be performed by a home nursing (HN) professional at the participant's home or nursing center to improve access and convenience for participants participating in the study. The Sponsor has selected a healthcare company that is responsible for providing HN services for participating sites (the HN vendor). The HN vendor is responsible for ensuring that all HN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that HN services are appropriate for a participant and the participant gives written informed consent to participate in HN visits, the HN network communicates with the participant and the participant's site. HN visits are scheduled on specified visit days to allow relevant assessments to be performed by the HN professional. The schedule of activities (see Appendix 1) specifies which assessments may be performed by an HN professional.

4.5.1 Informed Consent Forms and Screening Log

All participants and study partners must review, sign, and date the most current IRB/EC-approved written informed consent for participation in the study before any study-specific prescreening assessments, screening tests or evaluation are performed. Informed Consent Forms for enrolled participants and their study partners and for those who are not subsequently enrolled will be maintained at the study site.

All prescreening and screening evaluations must be completed and reviewed to confirm that participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants prescreened and screened and to confirm eligibility or record reasons for screening failure, as applicable. Prescreening is optional and is covered by a dedicated Informed Consent Form.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), smoking history, use of alcohol, and drugs of abuse. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant within 3 months prior to screening visit will be recorded. Demographic data will include age, sex, and self-reported race/ethnicity. Medical history and demographic data will be collected at the screening visit only.

As this study is being conducted in multiple geographic regions, it is likely that participants of different ethnic origins will be enrolled in the study. Although there is currently no indication that gantenerumab is metabolized or eliminated differently or that the treatment effect would be different in participants of different ethnic origins, collecting this information is essential to adequately evaluate the results of this study (e.g., possible differences in PK exposure [concentration of the drug in the blood] or treatment effect).

4.5.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary (optional), and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

The schedule of activities indicates when complete physical examinations (including neurological systems) are to be recorded (see Appendix 1).

Limited, symptom-directed physical examinations should be performed per the schedule of activities (or as clinically indicated). Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

In addition, weight will be obtained at screening, and at every visit at which creatinine clearance is tested as well as at any other visit as deemed necessary by the investigator. Height will be obtained at screening only.

4.5.4 Vital Signs

Vital signs will include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements.

Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

Vital sign measurements may be performed by an HN professional.

The schedule of activities indicates when vital signs (blood pressure and pulse rate) are to be recorded (see Appendix 1).

4.5.5 Cognitive, Functional, and Health Economics Assessments

The assessments described in this section will be performed as outlined in the schedule of activities (see Appendix 1) and in the order specified in Section 4.6.

Whenever possible, there should be consistency in the rater and study partner who complete the scales for each participant throughout the duration of the study. Potential raters will receive training and be approved by the rating scale contract research organization (CRO) prior to being allowed to administer any cognitive assessments or rating scales in the study.

Whenever possible, cognitive and functional assessments should be performed at the visit timepoints indicated in the schedule of activities (see Appendix 1). However, in exceptional circumstances for post-randomization visits, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per the schedule of activities, they may be performed up to 4 weeks out of window.

Given that the primary outcome measure in this trial involves subjective judgment, the adequacy of participant and study partner interviews and ratings will be monitored by an endpoint reliability program administered by the rating scale vendor; this is considered an essential part of good research methodology. For the primary endpoint as well as for some other scales, audio recordings may be used for quality assurance purposes. Prior studies have clearly demonstrated that the failure to adequately monitor such ratings can substantially increase the risks of failed trials (Becker and Greig 2008; Kobak 2010).

4.5.5.1 Clinical Dementia Rating Scale

The CDR global score (CDR-GS) characterizes a participant's level of impairment according to the following categories: 0 (normal), 0.5 (very mild dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia). The SOB score is a detailed quantitative general index that provides more information than the CDR-GS in

participants with mild dementia (Berg 1988; Morris et al. 2001, O'Bryant et al. 2010) and is scored from 0–18 with higher scores indicating greater impairment. The CDR characterizes six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The necessary information to make each rating is obtained through a semi-structured interview with the participant and a reliable informant or collateral source (e.g., a study partner).

As much as is feasible, the CDR should be administered to an individual participant by the same assessor throughout the study and that assessor should not perform the MMSE, ADAS-Cog, Verbal Fluency Task, Coding, FAQ, or Alzheimer's Disease Cooperative Study Group–Activities of Daily Living (ADCS-ADL). However, if in exceptional circumstances only this assessor is available to perform these other scales, then the CDR participant interview must be completed after the study partner interview but before ADAS-Cog, MMSE, Verbal Fluency Task, Coding, and other scales are completed. Nevertheless, at screening, baseline, Week 104, Week 116 or Week 128 (if applicable), the CDR rater cannot perform other scales than the CDR. In addition, the CDR rater should not be involved in safety assessments and especially should not receive information about any ARIA findings.

4.5.5.2 Alzheimer's Disease Assessment Scale–Cognitive Subscale

The ADAS-Cog is the most frequently used scale to assess cognition in clinical trials for mild to moderate AD dementia (Rozzini et al. 2007; Connor and Sabbagh 2008; Ihl et al. 2012). More specifically, the ADAS-Cog is a participant-based assessment that measures learning and memory, language production, language comprehension, constructional praxis, ideational praxis, and orientation. The modified version will be used; it has 13 items and includes the addition of delayed word recall and a number of cancellation subtests, as well as use of only one trial for word recognition (Mohs et al. 1997). Equivalent alternate forms of the word recall, word recognition, and number cancellation subtests will be used in successive test administrations.

4.5.5.3 Mini-Mental State Examination

The MMSE is a set of standardized questions used to evaluate possible cognitive impairment and help stage the severity level of this impairment (Folstein et al. 1975). The questions target six areas: orientation, registration, attention, short-term recall, language, and constructional praxis/visuospatial abilities. The MMSE is a participant-based assessment.

4.5.5.4 Free and Cued Selective Reminding Test–Immediate Recall

The FCSRT-Immediate Recall (FCSRT-IR) is a participant-based assessment that measures memory under conditions that control attention and cognitive processing. Impairments in FCSRT-IR performance have been associated with preclinical and early dementia in several longitudinal epidemiological studies (Grober and Buschke 1987; Sarazin et al. 2007). The 16-word version of the test will be used in this study.

4.5.5.5 Verbal Fluency Task

The category verbal fluency (e.g., animals) is a participant-based assessment that measures speed and flexibility of verbal thought. Verbal fluency tests are sensitive tools for detecting dementia (Pasquier et al. 1995; Lezak et al. 2004) and for monitoring decline over time (Clark et al. 2009).

4.5.5.6 Coding

The Coding, also called Digit Symbol Substitution Test (or DSST), is a subtest from the Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV; Wechsler 2008). The Coding is a participant-based assessment that measures speed of processing and associative memory. The test is known to be sensitive to disease progression (Lezak et al. 2004). The 120-second version of the test will be used in this study.

4.5.5.7 Functional Activities Questionnaire

The FAQ (Pfeffer et al. 1982) is an informant-based measure of functional abilities. Informants provide performance ratings of the target person on ten complex higher-order activities.

4.5.5.8 Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory

The ADCS-ADL (Galasko et al. 1997) is the scale most widely used to assess functional outcome in participants with AD (Vellas et al. 2008). The ADCS-ADL is a 23-item informant-based questionnaire that covers both basic ADL (e.g., eating and toileting) and more complex ADL or instrumental ADL (e.g., using the telephone, managing finances, preparing a meal). It has a 4-week recall period. Total scores range from 0–78, with higher scores indicating better functioning.

4.5.5.9 Zarit Caregiver Interview–Alzheimer's Disease

The Zarit Caregiver Interview–Alzheimer's Disease (ZCI-AD) is a modified version of the Zarit Burden Interview, which was originally designed to reflect the stresses experienced by caregivers for people with dementia (Zarit and Zarit 1990). The modified version includes slight modifications in item and title wording (e.g., removal of "your relative" to refer directly to the participant, removal of "burden" from title) and the use of 11-point numerical rating scales. The ZCI-AD scale consists of 30 items and is completed by the study partner without involvement from the site staff. It has a 4-week recall period.

4.5.5.10 Quality of Life–Alzheimer's Disease

The Quality of Life–Alzheimer's Disease (QoL-AD) was developed to assess QoL in participants who have dementia (Logsdon et al. 1999, 2002). The QoL-AD consists of 13 items covering aspects of participants' relationships with friends and family, physical condition, mood, concerns about finances, and overall assessment of QoL. The total score is the sum of the 13 items and ranges from 13–52, with higher scores indicating better HRQOL.

In this study, the QoL-AD will be administered in a standardized, structured interview format to participants by investigative staff in order to gather participant responses about QoL. The study partner will also complete the study partner version of the questionnaire to enable proxy responses from the study partner.

4.5.5.11 EQ-5D

The EuroQoL–Five Dimensions (EQ-5D) is a standardized measure of health status designed to provide a simple generic measure of health for clinical and economic appraisal. It is broadly applicable across a wide range of health conditions and treatment.

The EQ-5D assesses five domains to provide a health state index. These are anxiety/depression, pain/discomfort, usual activities, mobility, and self-care.

The following two versions will be used in this study:

- EQ-5D-5L Proxy, Version 1: The study partner (the proxy) is asked to rate the participant's health-related QoL in his or her (the proxy's) opinion.
- EQ-5D-5L, Self-Complete Version: The study partner is asked to rate his or her own health-related QoL.

4.5.5.12 Resource Utilization in Dementia Scale

The Resource Utilization in Dementia (RUD) scale (Wimo et al. 2003) aims to document formal and informal resource use in a clinical trial setting. The RUD-Lite captures the most important elements in dementia care: accommodation, informal care, hospitalizations, and community care services. Information on study partner sociodemographics in addition to working status and effect on productivity will be collected. The amount of informal care will be collected according to three types of care: personal ADL, instrumental ADL, and supervision. Data on accommodation and temporary changes in accommodation during the last month and the duration of these will be collected according to four levels of accommodation: own home, intermediate forms of accommodation, dementia-specific residential accommodation, and nursing home. Resource utilization will be recorded as the number of nights spent in different types of hospital wards, the number of visits to the most common types of outpatient care, and the number of visits in community care services.

4.5.5.13 Neuropsychiatric Inventory Questionnaire

The Neuropsychiatric Inventory–Questionnaire (NPI-Q) (Kaufer et al. 2000) was developed to assess a wide range of behaviors encountered in dementia participants, to provide a means of distinguishing severity of behavioral changes, and to facilitate rapid behavioral assessment through the use of screening questions. It is an informant-based instrument in which 12 behavioral domains are evaluated. The recall period is the past month, and severity scores range from 0–36, with higher scores indicating greater severity. The study partner's distress portion of the scale will not be used in this study.

4.5.5.14 Electronic Assessment of Rating Scales

The following rating scales will be captured electronically and transferred to the database directly from the core laboratory: ADAS-Cog, Verbal Fluency Task, ADCS-ADL, CDR, MMSE, FCSRT, FAQ, AD QoL, EQ-5D, RUD-Lite, NPI-Q, and CSSR-S.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

4.5.6.1 Standard Laboratory Samples

Samples for the following laboratory tests will be sent to a central laboratory for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

- Serum chemistry: AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory)

  HbA_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed according to the schedule of activities.
- Hematology: hemoglobin, hematocrit, RBC count (with morphology), WBC count, platelets, basophils, eosinophils, lymphocytes, monocytes, neutrophils, and WBC–other total counts.
- Screening serology: HIV, hepatitis B, and hepatitis C.
- Coagulation: PT.
- Urine for drugs of abuse: At screening only, urine samples will be analysed for the presence of the following drugs: amphetamine, benzodiazepines, cannabinoids, opiates, cocaine, barbiturates, and methadone. Results will be used to verify participant eligibility pertaining to drugs of abuse. Inconclusive results may be repeated once during the screening period. Investigators should use their best clinical judgment in cases where results may be erroneous (e.g., permitted use of opiates or ingestion of food/food supplements).
- Urinalysis: At screening only, urinalysis will be performed at the site by dipstick for blood, protein, glucose, and pH. Microscopic examination will be performed by the central laboratory if blood and/or protein results are positive or strongly positive.
- Urine for pregnancy test: Urine pregnancy testing will be performed at each dosing visit (prior to dose administration) for women of childbearing potential (including those who have had a tubal ligation), and at the site for any other female participants if required by local regulations. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory.

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

4.5.6.2 Biomarker Sampling

Samples will be obtained from all participants and will be used for research purposes to identify dynamic biomarkers that may be predictive of response to treatment with gantenerumab (in terms of dose, safety, and tolerability) and will help to better understand the pathogenesis, course, and outcome of AD and related diseases.

For participants who consent to the optional Roche Research Biosample Repository (RBR) residual biomarker samples will be kept for future biomarker research (see Section 4.5.12).

The procedures for the collection, handling, and shipping of biomarker samples are specified in the Sample Handling and Logistic Manual.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.12), biomarker samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Roche may keep information about screening test results, medical history, and demographic information for all participants (including non-eligible participants) for future development of diagnostic tests related to Aβ, *APOE* genotype, and AD, as well as additional analyses.

Cerebrospinal Fluid and Serum Sampling (for CSF-Enrolled Participants Only)

CSF samples and matching serum samples will be obtained from participants who choose to provide CSF samples during screening (CSF-enrolled participants) for confirmation of Aβ and tau levels for eligibility purposes (mandatory) and for monitoring Aβ and tau levels, as well as other CSF biomarkers at different timepoints during the study. The matching serum samples may be used to determine parameters that allow the assessment of the blood-brain barrier status and/or inflammatory processes in the brain, such as CSF/serum albumin ratio, CSF/serum IgG and IgM indices, and oligoclonal bands. CSF and serum samples will be collected according to the schedule of activities (see Appendix 1). Lumbar puncture will be performed by an individual who meets all local requirements and is proficient in the procedure. Lumbar puncture procedures and post–lumbar puncture care will be performed in accordance with local practice. CSF sampling should be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters. Procedures for the processing of the CSF samples can be found in the Sample Handling and Logistics Manual.

Approximately 12 mL of CSF will be collected at each timepoint. The sample will be divided into aliquots onsite and used for the following:

- Central measurement of gantenerumab levels in the CSF and biomarker analysis, including $A\beta_{1-42}$, t-tau, p-tau, as well as some exploratory markers. Samples may also be used to support the development of biomarker assays for diagnostic use.

Unused CSF samples will be kept for future biomarker research if the participant gives consent to participate in the RBR (see Section 4.5.12.5).

Clinical Genotyping

During screening, three mandatory 3-mL whole blood samples will be obtained for DNA extraction from every participant who has consented to participate in the study. All participants will be evaluated for *APOE* ε4 status, clusterin (apolipoprotein J) genotypes, and Fcγ-receptor genotype. The Fcγ-receptor genotype may play a role in PK and PD variability of antibody-based therapeutic agents and may be predictive of response and non-response.

APOE ε4 status will be determined and will be blinded to the Sponsor, investigator, and participant and will not be shared with the investigator or the participant until the study is unblinded (unless required for participant safety or by the relevant health authority or IRB/EC). Participants will have access to this information if they elect to at the end of the study. If already known, the *APOE* ε4 status will still need to be confirmed and should be kept blinded from the Sponsor. In addition, as much as possible, participant *APOE* ε4 status should remain blinded to the site and central MRI readers.

Samples and data may be used for future research or diagnostic test development.

RNA Sampling

During screening and at a subsequent visit as detailed in the schedule of activities (see Appendix 1), two 2.5-mL whole blood samples will be obtained for RNA extraction from every participant who has consented to participate in the study. The sample may be used to evaluate clusterin messenger RNA and other exploratory genetic markers in peripheral blood (see Section 4.5.12).

Plasma Sampling

At screening and at subsequent visits as detailed in the schedule of activities (see Appendix 1), two 6-mL whole blood sample will be obtained for plasma extraction from every participant who has consented to participate in the study.

This sample will be used to evaluate exploratory plasma biomarkers in peripheral blood, which may include, but will not be limited to Aβ, tau, $p\text{-}Tau,\ and$ neurofilament.

An additional plasma sample for the assessment of exploratory plasma biomarkers will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes

aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

4.5.6.3 Anti-Drug Antibody Sampling

Blood samples will be collected to assess the possible development of ADAs in all participants as noted in the schedule of activities (see Appendix 1). Plasma samples will be analysed for antibodies to gantenerumab using a bridging ELISA.

Samples collected from participants receiving placebo will not be assessed in the first instance but retained for subsequent analysis if appropriate.

Unused sample material may also be used for the purposes of current ADA assay improvement.

The procedures for the collection, handling, and shipping of ADA samples are specified in the Sample Handling and Logistics Manual supplied to the site.

4.5.6.4 Pharmacokinetic Sampling

Plasma Gantenerumab Samples

Blood samples will be collected to evaluate the pharmacokinetics of gantenerumab in plasma as noted in the schedule of activities (see Appendix 1).

An additional PK sample for the assessment of plasma concentrations of gantenerumab will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E, or occurrence of ARIA-H meeting discontinuation criteria.

Samples from participants receiving placebo may not be assessed at once but will be retained for subsequent analysis if appropriate. Samples will not be analysed in real time but will be batched for analysis throughout the study.

Unused sample material may be used for the purpose of current gantenerumab assay improvement, for the quantification of specific gantenerumab glycan species, and for the assessment of exploratory plasma biomarkers.

The procedures for the collection, handling, and shipping of PK samples are specified in the Sample Handling and Logistics Manual supplied to the site.

Cerebral Spinal Fluid for Assessment of Gantenerumab Concentration (for Participants Enrolled on the Basis of CSF Criteria Only)

For participants enrolled on the basis of CSF criteria and willing to perform lumbar puncture in the schedule of activities, an aliquot of CSF obtained by lumbar puncture, described in Section 4.5.6.2, will be allocated for the measurement of gantenerumab concentration. Samples from participants receiving placebo may not be assessed at once but will be retained for subsequent analysis if appropriate.

Unused sample material may also be used for the purposes of current assay improvement.

4.5.7 Electrocardiograms

Single 12-lead ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the participant has been resting in a supine position for at least 5 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws, brain MRI scans, and lumbar puncture). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site.

The centrally provided electrocardiograph machine should record the following: heart rate, QRS duration, and RR, PR, and QT intervals and transferred to the Sponsor database from the core laboratory.

4.5.8 Columbia–Suicide Severity Rating Scale

The C-SSRS (http://www.cssrs.columbia.edu) is an assessment tool used to assess the lifetime suicidality of a participant (C-SSRS at baseline) as well as any new instances of suicidality (C-SSRS since last visit). The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual or potential lethality. The C-SSRS baseline will be collected at baseline and the C-SSRS since the last visit will be collected at subsequent visits as indicated in the schedule of activities (see Appendix 1).

The assessment will be completed by a certified C-SSRS rater after he or she interviews the participant and the participant’s study partner during the study visit.

4.5.9 Brain Magnetic Resonance Imaging

MRI should be performed using 1.5-T or 3.0-T scanners, and wherever possible the same scanner should be used for an individual participant for the full duration of the study. MRI will be conducted at participant screening for safety monitoring, as a baseline measure of structural brain volumes, and as baseline information for the PET substudies (for the schedule of activities, see Appendix 1).

Where available, exploratory MRI techniques including rs-fMRI and DTI will also be acquired. In addition, the screening MRI will be used to help determine whether the exclusion criteria are met (e.g., number of microbleeds, presence of mass lesions).

MRI will be used during the study to help assess safety such as the occurrence of microbleeds or signs potentially indicative of inflammation or ARIA-E. Additional unscheduled MRI scans may be performed to better understand relevant CNS adverse events (such as increased confusion) occurring in the context of ARIA or to follow a sign that emerges at a scheduled scan; contrast agent may be used in such a case of follow-up MRI scans if administration of contrast agent is considered safe for the participant according to local standards. In addition, structural MRI (to assess whole brain and regional brain atrophy), fMRI, and DTI-MRI will be performed at multiple timepoints to determine potential treatment effects on MRI outcome measures (according to the schedule of activities).

MRI scans will include the following sequences:

- 3D T_1-weighted gradient recalled echo (GRE) scans
- T_2*-weighted GRE scans
- T_2-weighted FLAIR scans
- BOLD rs-fMRI, if available (to assess resting-state functional connectivity at investigative sites having the required software and sequences)
- DTI-MRI, if available (to assess fiber tract integrity)

For details on the specific imaging sequences and acquisition times required, refer to the MRI Manual.

MRI should not be performed unless at least 3 days have passed since a lumbar puncture. If an MRI and lumbar puncture are both scheduled for the same day, the MRI should be performed first.

All images (except BOLD fMRI and DTI-MRI) will be used to assess MRI inclusion and exclusion criteria.

MRI scans will be reviewed by a central MRI core laboratory, which will perform the diagnostic reads and assessment of MRI outcome measures. MRI scans should preferably be transferred to the central MRI core laboratory electronically. Data transfer from individual study sites to the central MRI core laboratory may take up to 7−10 days, if not done electronically. Upon receipt of the MRI scans from the study sites, the central MRI core laboratory will provide the diagnostic reads. MRI results must be made available to investigators prior to next dosing (refer to Section 5.1.2 for additional details on MRI safety management).

MRI facility qualification and scan quality control will be performed by the central MRI core laboratory.

Additional instructions regarding the procedures for MRI scan acquisition and transmittal to the central reading facility can be found in the MRI Manual.

4.5.10 Healthy Volunteer Magnetic Resonance Imaging Scans for Site Qualification

As part of site qualification, one to two volunteers (preferably two) at each site should be recruited and scanned using the same machine and the same sequences to be used for site qualification before any participant is scanned in this study. The choice of healthy volunteers is at the discretion of the investigator and/or the imaging center, and the volunteer must provide written consent to take part in the scanning calibration. Volunteers must not have any contraindications for MRI scanning (evaluation per local procedures at the imaging site), and they will not be enrolled in the study or undergo any other assessments as part of the trial. If volunteer scans are acquired, then they will be reviewed for suitable image quality and used for qualitative comparison with additional scans with the same volunteer acquired after certain events as follows: at the time of a major upgrade to the site's scanner, any other event deemed significant enough to affect image quality, or per central reader guidance. This procedure will help ensure consistency in scanning quality over the duration of the study. Two volunteers are ideal in case one volunteer is no longer readily available for test scanning.

Additional instructions regarding the procedures for MRI facility qualification can be found in the MRI Manual.

4.5.11 Positron Emission Tomography Scan

A PET scan will be performed for confirmation of Aβ levels for eligibility purposes in participants (PET-enrolled participants). Three radioligands are be used for screening purposes: [^{18}F] florbetapir (Amyvid™), [^{18}F] flutemetamol (Vizamyl™), and [^{18}F] florbetaben (Neuraceq™).

Screening PET scans must not be acquired prior, potentially exclusionary screening results are available in order to minimize radiation burden to participants. In order to allow sufficient flexibility for scheduling of the screening PET scan screening procedures (including central reading of the MRI scans) ideally should be completed within 2–3 weeks before the screening PET scan is required.

A positive PET scan using [^{18}F] florbetapir, [^{18}F] flutemetamol, or [^{18}F] florbetaben acquired outside this study protocol may be permissible to confirm participant inclusion with Medical Monitor approval. Previously acquired PET scans must meet quality standards detailed in the PET Technical Operations Manual and must be centrally evaluated.

Detailed instructions regarding the procedures for PET scan methodology, including scanning procedures can be found in the PET Technical Operations Manual.

4.5.12 Optional Samples for Research Biosample Repository

4.5.12.1 Overview of the Research Biosample Repository

The RBR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for participants in the future.

Specimens for the RBR will be retained from participants who give specific consent to participate in this optional research.

RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.12) will not be applicable at that site.

4.5.12.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to gantenerumab or AD:

- Leftover blood from Clinical Genotyping sample and clinical RNA sample and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), plasma biomarker sample, CSF samples, and serum samples

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing, or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analysed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.12.4 Confidentiality

Specimens and associated data will be labeled with a unique participant identification number.

Participant medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR specimens, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.12.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will

be required to document a participant's agreement to provide optional RBR specimens. Participants who decline to participate will not provide a separate signature.

The investigator should document whether or not the participant has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.12.6 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. If a participant wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the participant's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The participant will be provided with instructions on how to withdraw consent after the trial is closed. A participant's withdrawal from Study WN29922 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a participant's withdrawal from the RBR does not constitute withdrawal from Study WN29922.

4.5.12.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to participant participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TIMING OF STUDY ASSESSMENTS

4.6.1 Screening and Pretreatment Assessments

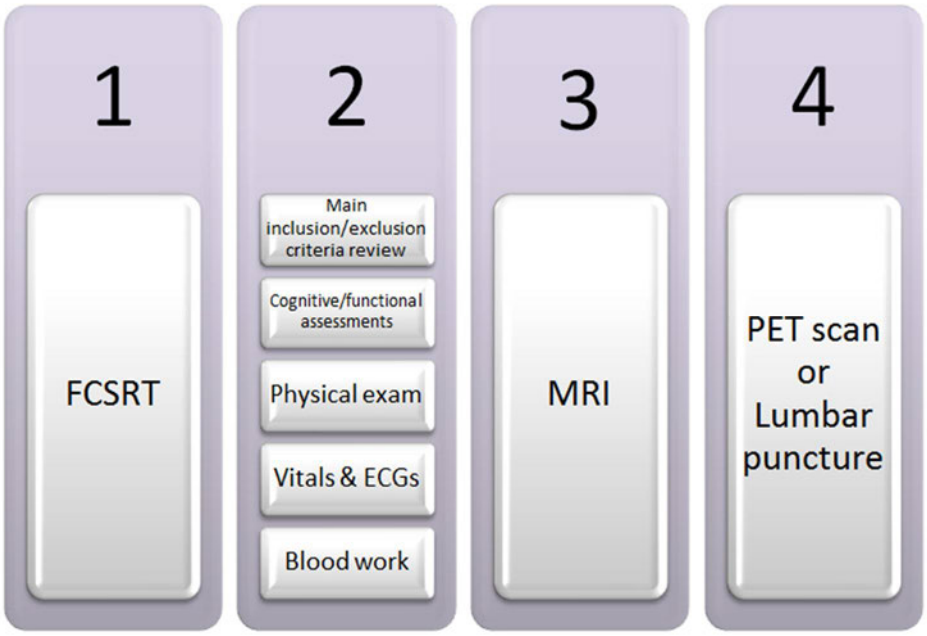
Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled participants and for participants who are not subsequently enrolled will be maintained at the study site. After providing written informed consent, participants who are willing to participate in the study will undergo all screening assessments within 12 weeks prior to the baseline visit, as detailed in the schedule of activities (see Appendix 1). Participants must fulfill all the entry criteria for participation in the study and the results must be available prior to the baseline visit.

The FCSRT and MMSE assessments may also be completed at prescreening. However, in this case, a separate prescreening consent would need to be signed and FCSRT and MMSE would not need to be repeated during the screening process. In case the participant would not qualify based on the FCSRT inclusion criteria, investigators have the option to repeat the FCSRT once after at least 6 months have elapsed if recruitment for the study is still ongoing. Rescreening of participants who failed MMSE is not allowed.

In case of an abnormal laboratory or ECG result at screening that may normalize upon retest, investigators have the option to repeat the tests (prior to baseline and within the 12-week screening window) once to confirm the test results before randomizing a participant at baseline.

In rare cases in which an MRI scan needs to be repeated or any other unexpected delay due to logistical or technical reasons, the screening period may be extended by some days. Extending the screening period beyond 12 weeks must be approved by the Medical Monitor and should be for exceptional circumstances only; careful scheduling should remain a priority.

The recommended order of screening assessments is as follows:



ECG = electrocardiogram; FCSRT = Free and Cued Selective Reminding Test; MRI = magnetic resonance imaging; PET = positron emission tomography.

The recommended order of clinical assessments and rating scales at screening is shown below.

Participant Assessments	Study Partner Assessments
1. FCSRT (performed at prescreening or at screening) 10-min break (optional) 2. MMSE (performed at prescreening or at screening) 3. CDR (participant interview)	CDR (study partner input)

CDR = Clinical Dementia Rating; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination.

CSF sampling, PET scan, and MRI scan at screening should be performed only once all other screening results are available and none exclude the participant from the trial.

If a participant does not qualify on the basis of applicable tests, the participant may be rescreened again after at least 3 months (6 months for FCSRT) have elapsed if recruitment for the study is still ongoing.

As noted in the exclusion criteria (see Section 4.1.2), participants may be rescreened after appropriate treatment if they were originally excluded for abnormal thyroid, folic acid, vitamin B-12, or HbA_{1c} results. Other laboratory tests that would exclude the participant may be repeated once (as an unscheduled laboratory assessment) if it is suspected that the abnormal result is transient and likely to be normal on repeat.

Participants may be rescreened if the protocol is amended such that they would satisfy the amended criteria and if recruitment for the study is still ongoing. In this case, all screening assessments must be repeated with the exception of lumbar puncture (if performed within the previous 12 months for this study and within eligible ranges) and PET scan within eligible ranges. Given that *APOE* status will not change over time, there is no need to repeat clinical genotyping in case of rescreening.

Participants may be rescreened if there is a substantial change in the participant's condition (e.g., a disallowed medication was stopped) and if recruitment for the study is still ongoing and all eligibility criteria are met.

It is suggested that screening tests with the exception of the lumbar puncture, MRI scan, and PET scan be performed within 1 to 2 weeks of signing the Informed Consent Form (to allow adequate time for the remaining tests). As soon as all the results are available, and none exclude the participant from the trial, CSF collection and/or PET scan and MRI scan should be performed, if required.

It will take several days to receive the results of the MRI or CSF. On occasion, the originally scheduled MRI or CSF collection day may need to be postponed and in the case of the MRI, it may need to be repeated. Therefore, the scheduling of these tests needs to be done carefully and should begin as soon as possible.

For participants enrolling on the basis of PET criteria, and for participants willing to participate in any of the PET substudies, scans can be obtained after all other screening results are available. For these participants, it is recommended that the MRI appointment should be scheduled to allow sufficient time for the PET scan to be performed and evaluated before the end of the screening period.

A positive PET scan using Amyvid™, Vizamyl™, or Neuraceq™ acquired outside this study may be permissible to confirm participant inclusion with Sponsor approval. Previously acquired PET scans must meet quality standards detailed in the PET Technical Operations Manual and must be centrally evaluated.

Roche may keep information about screening test results, medical history, and demographic information for all participants (including non-eligible participants) for future development of diagnostic tests related to Aβ, *APOE* genotype, and AD, as well as additional analyses.

4.6.2 Assessments at Baseline

In order to be randomized and to receive double-blind treatment, participants must have no significant change in medical, psychiatric, or neurological conditions or change in medication since screening. The recommended order of assessments and rating scales is as follows:

- Clinical assessments (e.g., CDR, MMSE, and ADAS-Cog), including all those that require study partner input, should be completed before any invasive safety assessments.
- Vital sign measurements, ECGs, blood draws for clinical laboratory assessments, PK, ADA, and plasma biomarker sampling, and urine samples are recommended to be conducted following scale assessments and must all be performed prior to study drug administration.

The recommended order of clinical assessments/rating scales at baseline is as follows:

Participant Assessments	Study Partner Assessments
1. ADAS-Cog13	1. CDR (study partner input)
2. CDR (participant interview)	2. FAQ
10-min break (optional)	3. ADCS-ADL
3. MMSE	4. ZCI-AD
4. Coding	5. QoL-AD
5. Verbal Fluency Task	6. EQ-5D
10-min break (optional)	7. RUD-Lite
6. QoL-AD	8. NPI-Q
7. C-SSRS	

ADAS-Cog13 = Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living; CDR = Clinical Dementia Rating; C-SSRS = Columbia–Suicide Severity Rating Scale; EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; NPI-Q = Neuropsychiatric Inventory–Questionnaire; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

If assessments are split over 2 days, all safety assessments must be performed on the same day as the study drug administration.

4.6.3 Assessments during the Double-Blind Treatment Period

In the double-blind treatment period, participants will receive up to 49 (in scenario 1) or 55 (in scenario 2, if applicable) SC administrations of study drug over the course of 114 or 126 (if applicable) weeks, respectively. The final on-treatment efficacy and safety assessments are scheduled 2 weeks after the last dose. Participants who have completed the double-blind treatment period at the time of the implementation of *the study extension by 12 weeks,* received up to 43 doses and underwent the final efficacy and safety assessments at Week 104, 2 weeks after the last dose.

The same recommended order of clinical assessments and rating scales as above for the baseline visit should be followed (omitting those that are not conducted per the schedule of activities; see Appendix 1). *However, in exceptional circumstances, for post-randomization visits, if the caregiver, the primary rater or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.*

Vital sign measurements, ECGs, blood draws for clinical laboratory assessments, PK, ADA, plasma biomarkers, and urine samples are *must be performed prior to study drug administration. They are also* recommended to be conducted following scale assessments.

If assessments are split over 2 days, all safety assessments must be done on same day as the treatment administration.

On each dosing day, after all assessments prior to dosing have been completed (see the schedule of activities in Appendix 1), gantenerumab or matching placebo will be administered subcutaneously at room temperature. For the first four doses, participants should be observed for a minimum of 2 hours after dosing and then for a minimum of 1 hour after all remaining doses (i.e., Doses 5 and beyond). Participants should leave the study center after injections only if they appear to be tolerating the injections. When doses are to be administered remotely from the clinical sites, study drug administration may be performed only by qualified health care providers, as defined by local regulations, who must remain with the participants for a minimum of 1 hour after each injection and be equipped with rescue medications.

Rescue medications to treat anaphylactic and anaphylactoid reactions must be available at the site or at the dosing location for HN visits. Participants and their study partners will be alerted to watch for signs of anaphylactic and anaphylactoid reactions and to contact the study center as soon as possible if any such signs are noted.

Visits at which the participant receives study drug may take place within ±7 days of the protocol-specified date for Q4W administration and ±3 days of the protocol-specified date for Q2W administration per the schedule of activities in Appendix 1. For Q4W injections, the recommended minimum time between doses is 3 weeks. The maximum recommended time between doses should not exceed 6 weeks. For Q2W injections, the recommendation is not to administer more than 1020 mg (i.e., 2 times 510 mg Q2W) within 28 days. Always return to initial planned schedule per randomization for subsequent visits.

All visits should be scheduled as close as possible to the exact day. It is preferred that all assessments for a visit be performed on the same day, but if necessary, assessments may be performed over more than 1 day. Preferably, all clinical scales and assessments should be performed on the same day. Study drug administration should be performed only after all assessments and rating scales for the participant have been completed.

For sites and participants for whom this is practical, visits that require only dosing, vital sign measurements, urine pregnancy test, C-SSRS assessment, and adverse event assessment may be performed at an alternate location conducted by appropriate health care professionals.

Refer to Appendix 1 for the schedule of activities during the treatment period.

4.6.4 Assessments during Open-Label Extension Period

The same recommended order of clinical assessments and rating scales as in the double-blind treatment period (see Appendix 1), as well as vital sign measurements,

ECGs, blood draws for clinical laboratory assessments, PK, ADA, plasma biomarkers, and urine samples *must be performed prior to study drug administration. They are also* are recommended to be conducted following scale assessments. If assessments are split over 2 days, all safety assessments must be performed on the same day as the treatment administration.

On each dosing day, after all assessments prior to dosing have been completed (see Appendix 1), gantenerumab and/or matching placebo will be administered subcutaneously at room temperature. For the first eight doses, participants should be observed for a minimum of 2 hours after dosing and then for a minimum of 1 hour after all remaining doses (i.e., doses 9 and beyond). Participants should leave the study center after injections only if they appear to be tolerating the injections. When doses are to be administered remotely from the clinical sites, study drug administration may be performed only by qualified health care providers, as defined by local regulations, who must remain with the participants for a minimum of 1 hour after each injection and be equipped with rescue medications.

Rescue medications to treat anaphylactic and anaphylactoid reactions must be available at the site or at the dosing location for HN visits. Participants and their study partners will be alerted to watch for signs of anaphylactic and anaphylactoid reactions and to contact the study center as soon as possible if any such signs are noted.

In the OLE, visits at which the participant receives study drug may take place ±3 days of the protocol-specified date for Q2W administration per the schedule of activities in Appendix 1. Always return to the initial planned schedule per randomization for subsequent visits.

For sites and participants for whom this is practical, visits that require only dosing, vital sign measurements, urine pregnancy test, C-SSRS assessment, and adverse event assessment may be performed at an alternate location conducted by appropriate health care professionals.

Refer to Appendix 1, Table 3 for the schedule of activities during the OLE.

4.6.5 Procedures for New MRI Findings

In addition to any local reading according to local procedures and requirements, all MRI scans will be reviewed by an expert central reader within approximately 1 week of receipt and a report provided to the site. For the purposes of overall study relevant decisions and recommendations, including participant eligibility as well as for analysis, results from the expert central reader will be used. Any time the central reader identifies a new MRI finding the study center medical staff and the Sponsor will be rapidly notified (see Section 4.5.9).

Refer to Section 5.1.2 for instructions in the event of new MRI findings (ARIA-E and ARIA-H).

4.6.6 Assessments at Study Completion or Early Termination Visit

Participants who complete the double-blind treatment period at Week 114 in scenario 1 or at Week 126 in scenario 2 (if applicable) will have to complete the final efficacy and safety assessment period 2 weeks following the last dose. Some participants may have already received the last study drug administration at Week 102 and performed the final efficacy and safety visit at Week 104 at the time of implementation of *the study extension by 12 weeks.*

All participants will be asked to come back for the follow-up assessments 14 weeks and 50 weeks after the last dose, unless they are transitioning to an OLE.

All participants who withdraw from treatment or discontinue from the study early (during the double-blind treatment period or during the OLE) will be asked to return 2 weeks after the last dose of study drug in order to complete the early termination visit.

In addition, participants who withdraw from treatment will be asked to return for collection of safety (except MRI) and limited efficacy data (i.e., the primary and secondary endpoints) at visits that have efficacy assessments per the schedule of activities until the end of the double-blind treatment period or until the last OLE follow-up visit (OLE Follow up 2) for those who enrolled in the OLE period.

Autopsy reports, including cause of death, for all participants who die during the study (i.e., prior to the Week 50 follow-up visit) should be requested.

Refer to the schedule of activities to be performed at the study completion in Appendix 1.

4.6.7 Follow-Up Assessments

Participants who complete the double-blind treatment period and who are not willing to enroll in an OLE or these who complete the OLE period (defined as administration of at least three 510-mg doses Q4W) and are not willing to enroll in the WN42171 open-label study will be asked to return to the clinic 14 weeks and 50 weeks after the last dose of study drug for the follow-up visits (Follow Up 1 and Follow Up 2 or OLE Follow Up 1 and OLE Follow Up 2, respectively)..

When participants complete the treatment period or discontinue early, every effort should be made to ensure that the safety follow-up period and all related assessments are completed.

After the study completion or early termination visit, adverse events should be followed as outlined in Sections 5.5 and 5.7. Refer to the schedule of activities (see Appendix 1) for the list of assessments to be performed at the follow-up visits.

4.6.8 Unscheduled Assessments

Assessments at unscheduled visits should be determined by the investigator based on clinical relevance and appropriateness to the cause of the unscheduled visit. The schedule of activities in Appendix 1 allows for all assessments to be performed at unscheduled visits.

4.7 TREATMENT, PARTICIPANT, STUDY, AND SITE DISCONTINUATION

4.7.1 Study Treatment Discontinuation

Participants must discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the participant
- Pregnancy
- Upon evidence of more than 15 ARIA-H, cumulatively
- Any disseminated leptomeningeal hemosiderosis

All participants who withdraw from treatment will be asked to return 2 weeks after last dose in order to complete the early termination visit assessments.

In addition, participants who withdraw from treatment will be asked to return for collection of safety (except MRI) and limited efficacy data (i.e., the primary and secondary endpoints) at visits that have efficacy assessments according to the schedule of activities until the end of the double-blind treatment period, *and then the follow-up visits*, or until the last OLE follow-up visit (OLE Follow Up 2) for those who enrolled in the OLE.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue study treatment prematurely will not be replaced.

4.7.2 Participant Discontinuation

Participants have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a participant from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Participant withdrawal of consent at any time
- Study termination or site closure
- Any medical condition that the investigator *and* Sponsor determines may jeopardize the participant's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the participant

- Participant non-compliance with the study and/or study procedures, defined as missing more than three consecutive dose administrations (with Q4W dosing regimen) or more than six consecutive dose administrations (with Q2W dosing regimen) because of non–safety-related reasons or more than half of the dosing visits in a calendar year

All participants who discontinue from the study early will be asked to return 2 weeks after last dose in order to complete the early termination visit.

Participant should be informed of circumstances under which their participation may be terminated by the investigator without the participant's consent. Any administrative or other reasons for withdrawal must be explained to the participant.

Every effort should be made to obtain information on participants who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, participants will not be followed for any reason after consent has been withdrawn.

Participants who withdraw from the study will not be replaced.

4.7.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.
- Futility analyses suggesting that treatment with gantenerumab is likely not effective.
- Sponsor determines it is the best interest of the participants.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.7.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all participants have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Gantenerumab is not yet approved, and clinical development is ongoing. The safety plan for participants in this study is based on clinical experience with gantenerumab in completed and ongoing studies. The identified risks for gantenerumab are outlined below. Please refer to the Gantenerumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of participants enrolled in this study. Eligibility criteria have been designed to exclude participants at higher risk for imaging-related abnormalities. Participants will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Gantenerumab

5.1.1.1 Amyloid-Related Imaging Abnormalities

To date, clinical experience with gantenerumab reveals that ARIA events are dose-dependent and *APOE* ε4 dependent. These events are manageable with MRI monitoring and dose intervention algorithms. In addition, in case of clinical symptoms, the use of IV glucorticosteroids may be considered.

Rules for management of participants who develop ARIA-E or ARIA-H are provided in Appendix 6.

5.1.1.2 Injection-Site Reactions

Gantenerumab may cause a reaction when given as an SC injection. In studies with gantenerumab, the most common events occurring more frequently with gantenerumab than with placebo were local ISRs, such as injection-site erythema. The majority of events were of mild intensity and resolved without treatment (see Section 1.2.3 for details).

Detailed information on the characteristic signs and symptoms of ISRs (e.g., erythema, pruritus) will be recorded on the dedicated eCRF page (see Section 5.3.5.2 for details on recording of ISRs).

5.1.1.3 Immunogenicity

As with administration of any exogenous protein, there is the potential for the development of ADAs, which can be neutralizing and/or sensitizing and which can potentially lead to febrile or allergic reactions, including anaphylaxis. The immunogenic risk of gantenerumab is considered low since it is a fully human antibody.

There are no clinical findings indicative of an immunogenic response to gantenerumab. Participants should be told how to recognize the signs and symptoms of hypersensitivity reactions and be monitored.

5.1.2 Management of Participants Who Experience Selected Adverse Events

Participants will undergo brain MRI examinations prior to every dose increase (pre-uptitration MRI scans) and according to the schedule of activities once the target dose is achieved. The pre-uptitration MRI scans will determine eligibility for the next uptitration dose. In the double-blind treatment period, a minimum of 3 doses of each dosing step have to be administered before the participant is eligible for the next uptitration dose. In the OLE, a minimum of 3 doses of each dosing step must be administered prior to be eligible for uptitration. In the OLE, a dose is defined as two consecutive dosing visits (one with an even dose number and one with an odd dose number, see Table 4, Section 4.3.2.2).

Participants will be eligible for uptitration if there are no new ARIA-E, if the ARIA-E is resolved (BGTS=0), and if the criteria for discontinuation because of ARIA-H have not been met.

In addition, the following dose adjustment and discontinuation rules for MRI findings will apply:

- In case of asymptomatic ARIA-E ≥1 and <4 BGTS: Continue study drug at the same dose level (i.e., do not uptitrate) and repeat MRI 4 weeks later.

  As long as BGTS is <4 and ≥1, continue study drug at the same dose level and continue MRI monitoring at 4-week intervals until the event resolves. When ARIA-E resolves, resume uptitration and MRI monitoring according to the schedule of activities.

  If BGTS ≥4 or symptoms develop, refer to the rule below.

- In case of occurrence of symptoms in the presence of ARIA-E (any size) or asymptomatic ARIA-E with ≥4 BGTS: Temporarily interrupt study drug (but continue all assessments per schedule of activities) and implement MRI monitoring performed at 4-week intervals until symptoms and ARIA resolve.

  When symptoms and ARIA-E resolve, reintroduce study drug at the next scheduled dosing visit, at the same dose given at the time the event was detected and perform an MRI scan after the first dose for participants on Q4W regimen and after the second dose for participants on the Q2W regimen.

  If no new ARIA-E is detected, resume uptitration and obtain an MRI scan per the titration schedule. For participants on the Q2W regimen, perform another MRI scan 3 months after study drug reintroduction.

- In exceptional cases of 1) an ARIA-E that is asymptomatic with BGTS <4 and that is considered stable over consecutive MRI images by the Sponsor and investigator; or 2) symptomatic ARIA-E for which the imaging evidence of ARIA-E has resolved but

the CNS symptoms continue, the study drug can either be reintroduced or uptitrated, as applicable, and 4-weekly MRI monitoring may no longer be necessary, as determined by the Sponsor and investigator.

- Symptomatic ARIA-E is defined as onset or worsening of CNS symptom(s) that is/are temporally associated with ARIA-E MRI findings.
- Any recurrence of ARIA-E: Treat using the same procedures as for the first event (based on symptoms and BGTS).
- Participants who develop $>$15 ARIA-H cumulatively will be discontinued from study drug (the cumulative number should not include any disseminated leptomeningeal hemosiderosis, i.e., up to 3 focal leptomeningeal hemosiderosis *either on the same scan or cumulatively*; a focal leptomeningeal hemosiderosis is counted as an ARIA-H).
- In cases where both ARIA-E and ARIA-H occur, the most conservative approach should be followed.
- A PK sample and a plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or ARIA-H that meet the discontinuation criteria.
- The investigators may choose to perform additional MRI monitoring for ARIA at any time.
- MRI monitoring of ARIA findings should be conducted at approximately 4-week intervals.
- Any other new significant findings will be reviewed by the medical monitor and appropriate dose action will be taken.

The iDMC reviews the incidence of ARIA in an unblinded manner and may recommend adjustment of dosing regimen and/or ARIA management for the overall study population or for a specific *APOE* ε4 genotype.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a

pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the participant at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.12)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the participant's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe; the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.8)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.2.4 Selected Adverse Events

Data on associated symptoms and safety MRI scans will be collected for the following selected adverse events:

- ARIA-E: ARIAs suggestive of vasogenic edema and sulcal effusions
- ARIA-H: ARIAs suggestive of microhemorrhages and/or hemosiderin deposits

Please refer also to Section 5.3.5.1 for further details how to report ARIA events.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4). The investigator is also responsible for reporting medical device complaints (see Section 5.4.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each participant contact. All adverse events, whether reported by the participant, the study partner, or noted by study

personnel, will be recorded in the participant's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

In addition, after administration of a PET ligand, but prior to initiation of study drug, the following adverse events should be reported:

- All adverse events (serious or non-serious) believed to be related to a PET ligand
- All serious adverse events occurring within 48 hours of PET ligand administration regardless of relatedness to the PET ligand

For reporting of serious adverse events, see Section 5.4.2 for instructions. For non-serious PET ligand adverse events, a PET ligand specific non-serious adverse event reporting paper form should be completed and submitted to the Sponsor or its designee by scanning and emailing the form using the email address provided on the form.

After initiation of study drug, all adverse events will be reported until the participant's last visit (including long-term follow-up visits).

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all participant evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

Table 5 provides guidance for assessing adverse event severity.

Table 5 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating “yes” or “no” accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 ARIA Findings

Not every ARIA finding qualifies as an adverse event. An ARIA finding must be reported as an adverse event if it meets any of the following criteria:

- Symptomatic ARIA-E (i.e., accompanied by CNS symptoms), and/or
- ARIA findings that result in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation), and/or

- Findings that are otherwise clinically significant in the investigator's judgment.

Any accompanying symptoms should also be captured as separate adverse events.

It is the investigator's responsibility to review all ARIA findings.

Observations of the same clinically significant ARIA finding should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.2 Injection Reactions

Injection reactions (local and systemic) are defined as adverse events that occur during or within 24 hours after study drug administration that are judged to be related to the study drug injection.

For local reactions, the diagnosis of injection site reaction should be captured on the Adverse Event eCRF, and associated signs and symptoms (e.g., erythema at injection site) should be recorded on the dedicated Injection Site Reaction eCRF.

Systemic reactions should be recorded as a single diagnosis on the Adverse Event eCRF (e.g., anaphylactic reaction). If possible, avoid ambiguous terms such as "systemic reaction."

5.3.5.3 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.4 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.5 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from “non-serious” to “serious,” providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.6 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator’s judgment

It is the investigator’s responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5× ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., “elevated potassium,” as opposed to “abnormal potassium”). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.7 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator’s judgment

It is the investigator’s responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.8 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy’s Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.9 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of AD.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed to progression of AD, "Alzheimer's disease progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.10 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.11 Lack of Efficacy or Worsening of Alzheimer's Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is because of disease progression, it should be reported as an adverse event.

5.3.5.12 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization due to expected progression of underlying disease
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The participant has not experienced an adverse event

5.3.5.13 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a study drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.14 Clinical Outcome Assessment Data

Adverse event reports will not be derived from clinical outcome assessment (COA) data by the Sponsor, and safety analyses will not be performed using COA data. Sites are not expected to review the COA data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Medical device complaints (see Section 5.4.4 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor: [redacted], *MBBS, PhD* (Primary)

Mobile Telephone No.: [redacted]

Medical Monitor: [redacted], *M.D., MSc* (Secondary)

Mobile Telephone No.: [redacted]

To ensure the safety of study participants, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours

per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.

In addition, the following serious adverse events should be reported after administration of a PET ligand and prior to initiation of study drug:

- All serious adverse events believed to be related to the PET ligand
- All serious adverse events occurring within 48 hours of the PET ligand administration, regardless of relatedness to the PET ligand.

The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until the participant's last visit (including long-term follow-up visits). Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Participants

Female participants of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 16 weeks after the last dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female participant exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 Reporting Requirements for Medical Device Complaints

The investigator must report all medical device complaints (e.g., devices for study drug administration) to the Sponsor. The investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward

the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the pharmacy manual for further details). If the medical device results in an adverse event to the study participant, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

5.5 FOLLOW-UP OF PARTICIPANTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the participant is lost to follow-up, or the participant withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as the participant's last study visit), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously

communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the reference safety information in the documents listed below:

Drug	Document
Gantenerumab	Gantenerumab Investigator's Brochure
[^{18}F] Florbetaben (Neuraceq™)	[^{18}F] Florbetaben Investigator's Brochure
[^{18}F] Flutemetamol (Vizamyl™)	[^{18}F] Flutemetamol Investigator's Brochure
[^{18}F] Florbetapir (Amyvid™)	[^{18}F] Florbetapir Investigator's Brochure
[^{18}F] GTP1	[^{18}F] GTP1 Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The purpose of this study is to investigate the treatment effect of gantenerumab relative to placebo. The primary efficacy analysis will be based on an intent-to-treat (ITT) population, which will include all randomized participants during the global enrollment phase, with participants grouped according to their randomly assigned treatment.

Approximately 1016 participants will be randomized in the global enrollment phase of this study. An increase in sample size may be considered in case of changes to sample size assumptions based on blinded data review or factors external to the study.

If at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA during the global enrollment phase, additional participants may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in the China.

The primary analyses of this study will include participants enrolled during the global enrollment phase; data from participants enrolled during the China extension will not be included in the primary analyses.

Details of the planned statistical analyses mentioned below will be fully specified in a separate SAP, which will be finalized prior to the locking and unblinding of the study database.

6.1 DETERMINATION OF SAMPLE SIZE

Determination of sample size is based on participants enrolled in the global enrollment phase. In this study, approximately 1016 participants will be enrolled and randomized in 1:1 ratio to each treatment arm (gantenerumab or placebo) during the global enrollment phase. A sample size increase may be considered if factors external to the study or blinded study data review would warrant a change to the sample size assumptions.

Additional participants may be randomized during the China extension if at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA during the global enrollment phase.

The estimated sample size required to demonstrate efficacy with regard to CDR-SOB is based on the following assumptions:

- The mean change in the CDR-SOB from baseline to Week 104 is 2.5 points in the placebo arm
- A common standard deviation across treatment arms for change of approximately 2.97 from baseline to Week 104 in the CDR-SOB
- Gantenerumab has a true effect of a 30% relative reduction in deterioration of CDR-SOB

Based on these assumptions, and using a student's T-test with equal variance, a sample size was calculated for 90% power to detect a true treatment effect of 30% relative reduction in deterioration of CDR-SOB at a two-sided α of 0.05.

Uncertainties on parameters affecting the power (e.g., dropout rate, study drug discontinuation rate, standard deviation, and placebo decline) were assumed to be equivalent to a drop-in sample size of up to around 35% and were corrected for accordingly. This calculation leads to a total of 1016 participants in the study.

At the date of writing Protocol Version 4, it is expected that participants *would have* miss*ed* an average of 8 weeks of study drug administration over the course of the original 2-year study due to the COVID-19 pandemic. This has the potential to decrease the power of the study from ~90% to ~80%. To mitigate the impact of missed administrations, the double-blind treatment period *was* extended by 12 weeks. Under current assumptions, this brings the study power back to the originally planned ~90%.

The sample size may be increased from 1016 up to 1322 participants (661 participants per arm). The decision whether to increase sample size will be based on blinded study data review, e.g., by a review of the frequency of missed study drug administrations due to the COVID-19 pandemic. Further details will be described in the SAP. The

assessment will be performed by the Sponsor at a specified timepoint. The sponsor will remain blinded. The sample size will not be reduced on the basis of this assessment. Other factors external to the study may also trigger a decision to increase sample size.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, participant disposition, and incidence of protocol deviations will be summarized for the ITT population according to the randomly assigned treatment arms.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (such as age, sex, race, disease stage, *APOE* ε4 status, use, and non-use of background therapy for AD) will be summarized descriptively for the ITT population, grouped according to the assigned treatment arm.

Descriptive summaries of continuous data will present the mean, standard deviation, median, and minimum and maximum. Descriptive summaries of discrete data will include frequencies expressed in terms of number and percentage of participants.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will use the ITT population, with participants grouped according to the treatment assigned at randomization.

6.4.1 Primary Efficacy Endpoint

The primary efficacy outcome measure is the change in CDR-SOB from baseline (Day 1) to Week 116. In the case where the double-blind treatment period is extended for an additional 12 weeks, the primary efficacy outcome measure will be the change in CDR-SOB from baseline (Day 1) to Week 128.

The clinical question of interest is to assess the study treatment effect on disease progression up to Week 116 (or Week 128, if applicable), irrespective of use or initiation of symptomatic treatments for AD, in the absence of the COVID-19 pandemic.

In accordance with the estimand framework outlined in the ICH-E9 addendum (EMA 2018), the attributes of the estimand for the primary endpoint are defined as follows:

- *Population: early (prodromal to mild) AD population including all randomized participants.*
- *Variable: change from baseline at Week 116 (or Week 128) in the CDR-SOB*
    - *Treatment: prescribed study drug including uptitration to the target dose, irrespective of use or initiation of symptomatic treatment for AD.*
- *Intercurrent events (ICE): the list of ICE will be defined in the SAP, this includes:*
    - *Treatment discontinued for study drug or condition–related (SDCR) reasons (e.g., treatment-related adverse event or lack of efficacy):*

- *Treatment discontinued for non-SDCR (NSDCR) reasons (e.g. purely administrative reason)*

- *Population level summary: mean change from baseline to Week 116 (or Week 128, as appropriate) between gantenerumab-treated participants and placebo-treated participants.*

The primary estimand is a combination of a treatment-policy strategy and a hypothetical strategy (FDA 2017) to account for the different assumptions for each type of ICE, SDCR or NSDCR.

Full details of the primary estimand, and of the corresponding estimator and estimation methods (e.g. statistical model, multiple imputation for missing or excluded data points) will be provided in the SAP. Supplementary estimands may also be considered and will be defined in the SAP.

Every effort will be made to minimize missing data. Furthermore, the Sponsor *has made* every effort to expedite the implementation of *the 12 week extension to the double-blind treatment period*. If the study is extended by an additional 12 weeks (for a total extension of 24 weeks), the number of patients in scenario 1 (who will have missing Week 128 efficacy data) will be minimized.

Participants who discontinue early from study treatment will be asked to return for collection of safety and limited efficacy data (i.e., the primary and secondary efficacy endpoints) until the end of the double-blind treatment period and follow-up visits.

Descriptive summaries of the number of participants with missing data, the number of participants in each scenario, the timing, and reasons for discontinuation from the study will also be provided by treatment group.

Additional details will be documented in the SAP.

6.4.2 Secondary Efficacy Endpoints

The absolute change from baseline in the continuous secondary efficacy endpoints listed in Section 2, Table 2 (including cognition/function endpoints, global endpoints, disease pathology biomarkers, and endpoints measuring other AD symptoms and effects) will be analysed using *an approach* similar to that described above for the primary efficacy endpoint.

In order to protect the overall type I error rate for the study when incorporating the hypothesis testing of the primary endpoint and secondary endpoints into the analysis, the fixed sequence testing procedure (Westfall and Krishen 2001) will be used to adjust for multiple comparisons. The first endpoint that will be tested is:

- Change from baseline to Week 116 in CDR-SOB

In the case where the double-blind treatment period is extended for an additional 12 weeks, the primary efficacy outcome measure will be the change in CDR-SOB from baseline (Day 1) to Week 128.

The order of testing for other secondary endpoints will be defined in the SAP.

The treatment difference in the primary endpoint (the change from baseline to Week 116 in the CDR-SOB) will be tested at a two-sided 5% overall significance level. If this test result is statistically significant, the secondary endpoints will be tested for significance in the predefined order as specified in the SAP. If any test result is not statistically significant, testing of the subsequent endpoints will not occur.

6.4.3 Exploratory Efficacy Analyses

Subgroup analysis of efficacy results will be performed for subgroups defined by age, sex, race, stage of disease (prodromal AD vs. mild AD), *APOE* ε4 status, geographic region, use and non-use of background therapies for AD, and other clinically relevant factors at baseline.

The efficacy endpoints collected during the Study WN29922 open-label treatment phase and during Study WN42171 *may* be combined with data from the Study WN29922 double-blind treatment phase in order to evaluate change from baseline beyond the end of the double-blind treatment period and to evaluate the effect of a delayed start of treatment with gantenerumab.

6.4.4 Pharmacodynamic and Exploratory Biomarker Analyses

PD and exploratory biomarker endpoints will be analysed using descriptive statistics, subgroup analysis, or statistical models if appropriate. For longitudinally measured endpoints, the change from baseline and the difference between participants randomized to gantenerumab and participants randomized to placebo will be estimated if appropriate.

Prior to completion of the study a separate PD cutoff date may be established to allow expedient sample analyses and early access by third party vendors.

Exploratory biomarkers may be reported separately.

6.5 SAFETY ANALYSES

The safety-analysis population will include all randomized participants who receive at least one dose of study drug, with participants grouped according to the treatment actually received, as defined in the SAP.

- Incidence, nature, and severity of MRI safety findings: ARIA-E and ARIA-H
- Incidence, nature, severity, and timing of injection-site reactions
- Incidence, nature, and severity of serious adverse events
- Incidence, nature, and severity of adverse events

- Incidence of adverse events of special interest
- Incidence of treatment discontinuations due to adverse events
- Mean changes in clinical laboratory tests from baseline over time; incidence of treatment-emergent abnormal laboratory values and abnormal laboratory values reported as adverse events
- Mean change in ECG assessments from baseline over time and incidence of abnormal ECG assessments
- Physical and neurologic examination abnormalities
- Mean change in vital signs (blood pressure, pulse rate) from baseline over time and incidence of abnormal vital sign measurements
- Changes in CSSR-S scores from baseline over time
- Number and proportion of participants with ADAs during the study relative to the number and proportion of participants with ADAs at baseline

Prior to completion of the study a separate ADA cutoff date may be established to allow expedient samples analyses and early access by third party vendors. The ADA cutoff date will be applied when there is sufficient ADA sample data available to adequately assess immunogenicity.

6.6 PHARMACOKINETIC ANALYSES

Plasma concentration data for gantenerumab *may* be tabulated and summarized. Descriptive summary statistics will include the arithmetic mean, median, range, SD, and coefficient of variation, as appropriate. Because a sparse PK sampling design is being used, population (non-linear mixed-effects) modeling will be used to analyse the dose concentration–time data of gantenerumab. Information from other clinical studies may be incorporated to establish the PK model. The selection of parameters and the derivation of individual measures of exposure, such as AUC, C_{max}, and trough serum concentration, will depend on the final PK model used for this analysis. The influence of background medication on the pharmacokinetics of gantenerumab will be explored and, if appropriate, concentration–effect relationships may be assessed post hoc for PD, efficacy, or safety measures.

The results of this modeling analysis may be reported separately from the clinical study report.

CSF concentrations of gantenerumab *may* be tabulated and summarized as appropriate.

Prior to completion of the study a separate PK cutoff date may be established to allow expedient sample analyses and early access by third party vendors. The PK cutoff date will be applied when there is sufficient PK sample data available to adequately characterize PK.

Additional PK analyses will be conducted as appropriate and may be reported separately from the clinical study report.

6.7 INTERIM ANALYSIS

6.7.1 *Optional Futility Analysis*

*Sponsor may perform a*n interim analysis for futility approximately 116 weeks after 50% of the targeted study enrollment has been reached. If the study is extended by an additional 12 weeks, the interim analysis will be performed approximately 128 weeks after 50% of the targeted study enrollment has been reached. The exact timing of an interim analysis may be synchronized with Study WN39658.

An independent data coordinating center will be responsible for the interim analyses. The study results will only be reviewed by the iDMC *and the Sponsor will remain blinded. Other third party vendors may be involved in data preparation and analyses, as appropriate.*

The iDMC may recommend stop for futility if the failure criterion is met. The failure criterion will represent a low probability of a positive study outcome given the data observed at the time of interim analysis. *If the futility criteria are not met, the study continues beyond the interim analysis. The failure criterion will be pre-specified in the iSAP.*

Details of the futility analysis, including the final decision to conduct it, the rationale, timing, and statistical details for the analyses (such as the data that would be reviewed by the iDMC and futility thresholds) will be documented in the iSAP. This will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.

6.7.2 Optional Interim Analyses

Based on availability of information pertaining to gantenerumab or other compounds with similar mode of action that may emerge during the course of this study, the Sponsor may choose to conduct an additional interim analysis *which may include efficacy, safety and biomarker outcomes including amyloid PET SUVr and/or other biomarkers to confirm PD effect. This analysis may be done on a whole study population or in a well predefined subgroup when approximately 50% of the overall population has reached Week 116. If the study is extended by an additional 12 weeks, the interim analysis will be performed once approximately 50% of the overall population has reached Week 128.*

An independent data coordinating center will be responsible for the interim analyses. The study results will only be reviewed by the iDMC *and th*e Sponsor will remain blinded. *Other third party vendors may be involved in data preparation and analyses, as appropriate.*

The iDMC may indicate that a pre-specified success criterion has been met. If so, the Sponsor may decide to present the data to a health authority. Any interim, unblinded data will be strictly firewalled to ensure those involved in the conduct of the ongoing trial and the WN42171 OLE trial remain fully blinded. If needed, appropriate measures will be taken to control the overall Type I error rate and described in the SAP

Details of the interim analyses, including the decision to conduct the optional interim analyses, the rationale, timing, and statistical details for the analyses (such as the data that would be reviewed by the iDMC and efficacy thresholds) will be documented in an iSAP, and the iSAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.

6.8 CHINA EXTENSION ANALYSIS

The objective of the China extension and the China subpopulation analyses is to assess the treatment effects of gantenerumab in a population of participants enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA and to investigate the consistency in treatment effect between the China subpopulation and the global population for the purpose of registration in China.

All participants enrolled in the global enrollment phase in China will be included in the primary analysis. The analysis of the China extension will be conducted after the end of China extension and will be reported separately from the primary analysis and at a subsequent point in time. Details will be provided in the SAP.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. All electronic data from external vendors will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

COA data will be collected through the use of an electronic device (tablet) provided by a vendor. Some COA data may be audio recorded for quality assurance purposes. The

device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR, Part 11). The electronic data are available for view access only via secure access to an online Web portal. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive participant data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC CLINICAL OUTCOME DATA

Participants, study partners, and appropriate site staff will use an electronic device (tablet) to capture COA. For some COA, audio recordings may be used for quality assurance purposes. All data will be transmitted via Web automatically after entry into a centralized database maintained by the electronic device vendor.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive participant data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participant-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate

and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic COA data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Home Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each participant the objectives, methods, and potential risks associated with each optional procedure. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a participant's agreement to participate in optional procedures. Participants who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the participant or the participant's legally authorized representative before his or her participation in the study. The case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the participant to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Participants must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the participant or the participant's legally authorized representative. All signed and dated Consent Forms must remain in each participant's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include participant authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for participant authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the participant, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each participant enrolled in the study through assignment of a unique participant identification number. This means

that participant names are not included in data sets that are transmitted to any Sponsor location.

Participant medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Medical information may be given to a participant's personal physician or other appropriate medical personnel responsible for the participant's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the participant data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

The overall procedures for quality assurance of clinical study data are described in the Roche standard operating procedures. This study will be sponsored by F. Hoffmann-La Roche Ltd. Roche will provide clinical operations oversight, site monitoring and management, data management support, and medical monitoring.

Study drug distribution may occur through an IxRS (see Section 4.2). Central facilities may be used for study assessments (i.e., ECG, lumbar puncture, specified laboratory tests, PK, rating scales, and MRI and PET imaging, as applicable).

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in participants involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in participants involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to participants or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

Table 1: Week –12 to Week 32; Dose Escalation with Q4W Administration

Assessment/Procedure	Prescreen & Screening	Baseline	Dose Escalation Period									Unsched Visit
	Weeks –12 to –1	Day 1	Day 4	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	
Dose Number		1 [a]		2	3	4	5 [b]	6 [b]	7 [a]	8 [b]	9 [b]	
Dose level in milligrams (mg)		120		120	120	255	255	255	510	510	510	
Informed consent(s) [c]	x											
Review of inclusion and exclusion criteria	x	B										
Medical history, personal status, and demographics	x											
Weight and height [t]	x	x							x			x
Clinical genotyping samples	x											
Clinical RNA samples	x											
Urinalysis [d]	x											
Urine sample for drugs of abuse [e]	x											
Coagulation (PT)	x											
Viral serology (HIV, hepatitis B, and hepatitis C)	x											
FCSRT	P [f]											
12-Lead electrocardiogram [g]	x	B				B			B			x
PK plasma sample [h, v]		B	x						B			x
ADA sample		B							B			x
Serum chemistry [i] and hematology [j]	x	B							B			x
Plasma biomarker sample [u]	x								B			x
Complete physical examination (includes neurological systems) [k]	x											x

Appendix 1: Schedule of Activities (cont.)
Table 1: Week –12 to Week 32; Dose Escalation with Q4W Administration (cont.)

Assessment/Procedure	Prescreen & Screening	Baseline	Dose Escalation Period									Unsched Visit
	Weeks –12 to –1	Day 1	Day 4	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	
Dose Number		1 [a]		2	3	4	5 [b]	6 [b]	7 [a]	8 [b]	9 [b]	
Dose level in milligrams (mg)		120		120	120	255	255	255	510	510	510	
Limited physical examination [l]									B			x
MRI scan [m, n]	x [o]					B			B			x
CSF and matching serum sampling [m, p] or PET scan [m, p]	x											
CDR	P&SP	P&SP							P&SP			P&SP
ADAS-Cog13		P							P			P
Verbal Fluency Task		P							P			P
Coding		P							P			P
ADCS-ADL		SP							SP			SP
FAQ		SP							SP			SP
MMSE	P [f]	P							P			P
EQ-5D		SP							SP			SP
QoL-AD		P&SP							P&SP			P&SP
ZCI-AD		SP							SP			SP
RUD-Lite		SP							SP			SP
NPI-Q		SP							SP			SP
C-SSRS BL/SLV		P							P			P
Vital signs [q]	x	B	B	B	B	B	B	B	B	B	B	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [r]	x	B		B	B	B	B	B	B	B	B	x
Study drug administration [h, s]		x		x	x	x	x	x	x	x	x	

Appendix 1: Schedule of Activities (cont.)
Table 1: Week –12 to Week 32; Dose Escalation with Q4W Administration (cont.)

ADAS-Cog13=Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL=Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR=Clinical Dementia Rating; CSF=cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D=EuroQol-Five Dimensions; FAQ=Functional Activities Questionnaire; FCSRT=Free and Cued Selective Reminding Test; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; NPI-Q=Neuropsychiatric Inventory–Questionnaire; PET=positron emission tomography; PK=pharmacokinetic; Prescreen=prescreening; Q4W=every 4 weeks; QoL-AD=Quality of Life–Alzheimer's Disease; RBR=Research Biosample Repository; RUD-Lite=Resource Utilization in Dementia–Lite; SC=subcutaneous; Unsched=unscheduled; Wk=week; ZCI-AD=Zarit Caregiver Interview–Alzheimer's Disease.

B=before study drug administration; P=participant completion; P&SP=participant and study partner completion; SP=study partner completion.

Notes: The visit window is ±7 days for dosing days and +3 days for non-dosing Day 4. For Q4W injections, the recommended minimum time between doses is 3 weeks. The maximum recommended time between doses should not exceed 6 weeks. Participants should return to initial planned schedule per randomization for subsequent visits.

In case of rescreening a participant, all screening assessments must be repeated other than the lumbar puncture and amyloid PET testing if performed within the previous 12 months for this study and are within the eligible ranges. In addition, clinical genotyping will not need to be repeated in case of rescreening.

[a] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first, and within 1 week prior to the first dose at baseline. All safety assessments (e.g., vital signs, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, for post-randomization visits, if the caregiver, the primary rater or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.

[b] Visit suitable for home administration of gantenerumab.

[c] Participants in the optional prescreening period must provide written consent before any study-specific prescreening assessments are performed. If participant is eligible and decides to participate in the screening assessments, he or she will need to provide new written consent.

[d] Performed at the site by dipstick for blood, protein, glucose, and pH.

[e] Urine samples will be analysed for the presence of the following drugs: amphetamine, benzodiazepines, cannabinoids, opiates, cocaine, barbiturates, and methadone.

[f] Can be done at prescreening or at screening. There is no need to repeat the test at screening if performed at prescreening.

[g] Electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the participant has been resting in a supine position for at least 5 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws, brain MRI scans, and lumbar puncture). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

[h] Accurate recording of the date and time of study drug administration and PK sampling is critical.

[i] Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). During the screening period (Week –1 to Week –12), hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[j] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelets, basophils, eosinophils, lymphocytes, monocytes, neutrophils, and WBC–other total counts.

[k] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

[l] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[m] CSF and matching serum sampling, and PET and MRI scans at screening should be performed once all other screening results are available and none exclude the participant from the study.

[n] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. It is not recommended that the MRI be performed on the same day as the IMP administration (especially during uptitration period during which it is recommended to do the MRI at least 10 days after the third dose of sing step). MRI should be performed before or at least 3 days following a lumbar puncture.

[o] Includes resting-state functional MRI and DTI outcome measures where available.

[p] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters. For post-baseline visits, lumbar puncture as well as serum sampling should be performed prior to dosing. Only one method (CSF or PET) confirming amyloid is necessary for all participants.

[q] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[r] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[s] Study drug administration should be performed only after all assessments/rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by SC injection. Participants should be observed up to 2 hours after dosing. After the fourth injection visit, the observation time may be reduced to 1 hour. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[t] Height measured at screening only.

[u] A plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

[v] A plasma PK sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

Appendix 1
Schedule of Activities (cont.)

Table 2: Week 36 to the End of Study: 510 mg Q2W

												Only for Participants Who Have Completed Week 104 when *the 12 week study extension* is Implemented			
	Treatment Period										Final Efficacy and Safety Assessments	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
Assessment/Procedure	Wk 36	Wk 38	Wk 40	Wk 41	Wk 42–50	Wk 52	Wk 54–74	Wk 76	Wk 78–102	Wk 103	Wk 104 [a, b]	Wk 116	Wk 152		
Dose number	10	11	12		13–17 [c]	18 [a]	19–29 [c]	30 [a]	31–43 [c]						
Dose level in milligrams (mg)	510	510	510		510	510	510	510	510						
12-Lead ECG						B		B			x	x		x	x
PK plasma sample [d]				x (Site visit)		B		B		x (Site visit)		x	x	x	x
ADA sample						B		B				x	x	x	x
Clinical RNA sample											x			x	
Serum chemistry [e] and hematology [f]						B		B			x	x	x	x	x
Plasma biomarker sample [o]						B					x			x	x
Complete physical examination (including neurological systems) [g]											x			x	x
Limited physical examination [h]						B		B							x
Weight						x		x			x	x	x	x	x

Appendix 1: Schedule of Activities (cont.)
Table 2: Week 36 to the End of Study: 510 mg Q2W (cont.)

												Only for Participants Who Have Completed Week 104 when *the 12 week study extension* is Implemented			
	Treatment Period										Final Efficacy and Safety Assessments	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
Assessment/Procedure	Wk 36	Wk 38	Wk 40	Wk 41	Wk 42–50	Wk 52	Wk 54–74	Wk 76	Wk 78–102	Wk 103	Wk 104 [a, b]	Wk 116	Wk 152		
Dose number	10	11	12		13–17 [c]	18 [a]	19–29 [c]	30 [a]	31–43 [c]						
Dose level in milligrams (mg)	510	510	510		510	510	510	510	510						
MRI scan [i]	B				Wk 48 [j]		Wk 60	B			x [j]			x [j]	x
CSF [k] and matching serum sampling (for participants enrolled based on CSF eligibility criteria only)								x			x			x [k]	
CDR						P&SP		P&SP			P&SP		P&SP	P&SP	P&SP
ADAS-Cog13						P		P			P		P	P	P
Verbal Fluency Task						P		P			P		P	P	P
Coding						P		P			P		P	P	P
ADCS-ADL						SP		SP			SP		SP	SP	SP
FAQ						SP		SP			SP		SP	SP	SP
MMSE						P		P			P		P	P	P
EQ-5D						SP		SP			SP			SP	SP
QoL-AD						P&SP		P&SP			P&SP			P&SP	P&SP
ZCI-AD						SP		SP			SP			SP	SP
RUD-Lite						SP		SP			SP			SP	SP

Appendix 1: Schedule of Activities (cont.)
Table 2: Week 36 to the End of Study: 510 mg Q2W (cont.)

												Only for Participants Who Have Completed Week 104 when *the 12 week study extension* is Implemented			
	Treatment Period										Final Efficacy and Safety Assessments	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
Assessment/Procedure	Wk 36	Wk 38	Wk 40	Wk 41	Wk 42–50	Wk 52	Wk 54–74	Wk 76	Wk 78–102	Wk 103	Wk 104 [a, b]	Wk 116	Wk 152		
Dose number	10	11	12		13–17 [c]	18 [a]	19–29 [c]	30 [a]	31–43 [c]						
Dose level in milligrams (mg)	510	510	510		510	510	510	510	510						
NPI-Q						SP		SP			SP			SP	SP
C-SSRS BL/SLV						P		P			P			P	P
Vital signs [l]	B	B	B		B	B	B	B	B		x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [m]	B	B	B		B	B	B	B	B		x	x		x	x
Study drug administration [d, n]	x	x	x		x	x	x	x	x						

ADAS-Cog13=Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL=Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR=Clinical Dementia Rating; CSF=cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D=EuroQol-Five Dimensions; FAQ=Functional Activities Questionnaire; FCSRT=Free and Cued Selective Reminding Test; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; NPI-Q=Neuropsychiatric Inventory–Questionnaire; OLE=open-label extension; PET=positron emission tomography; PK=pharmacokinetic; Q2W=every 2 weeks; QoL-AD=Quality of Life–Alzheimer's Disease; RBR=Research Biosample Repository; RUD-Lite=Resource Utilization in Dementia–Lite; SC=subcutaneous; Unsched=unscheduled; Wk=week; ZCI-AD=Zarit Caregiver Interview–Alzheimer's Disease.

B=before study drug administration; P=participant completion; P&SP=participant and study partner completion; SP=study partner.

Appendix 1: Schedule of Activities (cont.)
Table 2: Week 36 to the End of Study: 510 mg Q2W (cont.)

Notes: The visit window is ± 3 days for dosing days and +3 days for Week 41 and Week 103 non-dosing days. For Q2W injections, the recommendation is not to administer more than 1020 mg (i.e., 2 times 510 mg Q2W) within 28 days. Participants should return to initial planned schedule per randomization for subsequent visits.

[a] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vitals, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.

[b] Transition to OLE study for participants who are eligible to participate.

[c] Visit suitable for home administration of gantenerumab.

[d] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria

[e] Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). At Week 52 and Week 104, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[f] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

[g] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary (optional), and neurological systems.

[h] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[i] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[j] Includes resting-state functional MRI and DTI outcome measures, where available.

[k] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For participants enrolling based on CSF eligibility criteria, CSF and matching serum samples are optional at Week 76. Lumbar puncture does not have to be performed the same day as the main Week 76 visit or Week 104 visit, but should be performed in a reasonable time around these visits. The need for CSF collection at early termination visit will be discussed on a case-by-case *based on the participant's condition and the time since last lumbar puncture and advice by the Medical Monitor may be sought.*

[l] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[m] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[n] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by subcutaneous injection (full details are provided in the pharmacy manual). Participants should be observed for up to 2 hours after dosing. After the fourth injection visit, this observation time may be reduced to 1 hour. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[o] A plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

Appendix 1
Schedule of Activities (cont.)

Table 3: Scenario 1 / Week 104 to the End of Study: 510 mg Q2W

(3-Month Extension)

Assessment/Procedure	Treatment Period			Final Safety and Efficacy Assessment	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
	Wk 104 [a]	Wk 106-114 [c]	Wk 115	Wk 116 [a, b]	Wk 128	Wk 164		
Dose number	44	45-49						
Dose level in milligrams (mg)	510	510						
12-Lead ECG	x			x	x		x	x
PK plasma sample [d]			x (site visit)		x	x	x	x
ADA sample					x	x	x	x
Clinical RNA sample	x			x			x	
Serum chemistry [e] and hematology [f]	x			x	x	x	x	x
Plasma biomarker sample [o]	x			x			x	x
Complete physical examination (including neurological systems) [g]				x			x	x
Limited physical examination [h]	x							x
Weight	x			x	x	x	x	x
MRI scan [i]	x [j]			x [j]			x [j]	x

Appendix 1: Schedule of Activities (cont.)

Table 3: Scenario 1 / Week 104 to the End of Study: 510 mg Q2W (3-Month Extension)

Assessment/Procedure	Treatment Period			Final Safety and Efficacy Assessment	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
	Wk 104 [a]	Wk 106-114 [c]	Wk 115	Wk 116 [a, b]	Wk 128	Wk 164		
Dose number	44	45-49						
Dose level in milligrams (mg)	510	510						
CSF [k] and matching serum sampling (for participants enrolled based on CSF eligibility criteria only)				x			x [k]	
CDR	P&SP			P&SP		P&SP	P&SP	P&SP
ADAS-Cog13	P			P		P	P	P
Verbal Fluency Task	P			P		P	P	P
Coding	P			P		P	P	P
ADCS-ADL	SP			SP		SP	SP	SP
FAQ	SP			SP		SP	SP	SP
MMSE	P			P		P	P	P
EQ-5D	SP			SP			SP	SP
QoL-AD	P&SP			P&SP			P&SP	P&SP
ZCI-AD	SP			SP			SP	SP
RUD-Lite	SP			SP			SP	SP
NPI-Q	SP			SP			SP	SP
C-SSRS BL/SLV	P			P			P	P
Vital signs [l]	x	x		x	x	x	x	x
Concomitant medications	x	x		x	x	x	x	x
Adverse events	x	x		x	x	x	x	x
Urine pregnancy test [m]	x	x		x	x		x	x
Study drug administration [d, n]	x	x						

Appendix 1: Schedule of Activities (cont.)

Table 3: Scenario 1 / Week 104 to the End of Study: 510 mg Q2W (3-Month Extension)

ADAS-Cog13=Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL =Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR =Clinical Dementia Rating; CSF =cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D =EuroQol-Five Dimensions; FAQ =Functional Activities Questionnaire; FCSRT=Free and Cued Selective Reminding Test; MMSE =Mini-Mental State Examination; MRI =magnetic resonance imaging; NPI-Q =Neuropsychiatric Inventory–Questionnaire; OLE=open-label extension; PET =positron emission tomography; PK =pharmacokinetic; Q2W =every 2 weeks; QoL-AD =Quality of Life–Alzheimer's Disease; RBR =Research Biosample Repository; RUD-Lite =Resource Utilization in Dementia–Lite; SC =subcutaneous; Unsched =unscheduled; Wk =week; ZCI-AD =Zarit Caregiver Interview–Alzheimer's Disease.

B =before study drug administration; P =participant completion; P&SP=participant and study partner completion; SP=study partner.

Notes: The visit window is ±3 days for dosing days and +3 days for Week 115 non-dosing days. For Q2W injections, the recommendation is not to administer more than 1020 mg (i.e., 2 times 510 mg Q2W) within 28 days. Participants should return to initial planned schedule per randomization for subsequent visits.

SoA from Week –12 to Week 103 for scenario 1 is described in Appendix 1, Table 1 and Table 2.

[a] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vitals, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.

[b] Transition to OLE study for participants who are eligible to participate.

[c] Visit suitable for home administration of gantenerumab.

[d] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

[e] Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). At Week 104 and Week 116, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[f] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

[g] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

[h] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[i] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[j] Includes resting-state functional MRI and DTI outcome measures, where available.

[k] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For participants enrolling based on CSF eligibility criteria, CSF and matching serum samples are optional at Week 76 ; lumbar

puncture does not have to be performed the day of Week 76 or Week 116 visit, but should be performed in a reasonable time around these visits; the need of CSF collection at early termination visit *should be determined on a case-by-case basis based on the participant's condition and the time since last lumbar puncture and advice from* the Medical Monitor may be sought.

[l] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[m] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[n] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by subcutaneous injection (full details are provided in the pharmacy manual). Participants should be observed for about 1 hour after dosing. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[o] A plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria

Appendix 1
Schedule of Activities (cont.)

Table 4: Scenario 2 / Week 104 to the End of Study: 510 mg Q2W (Additional 3-Month Extension)

Assessment/Procedure	Treatment Period			Final Safety and Efficacy Assessment	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
	Wk 104[a]	Wk 106-126[c]	Wk 127	Wk 128[a, b]	Wk 140	Wk 176		
Dose number	44	45-55						
Dose level in milligrams (mg)	510	510						
12-Lead ECG	x			x	x		x	x
PK plasma sample [d]			x (site visit)		x	x	x	x
ADA sample					x	x	x	x
Clinical RNA sample	x			x			x	
Serum chemistry [e] and hematology [f]	x			x	x	x	x	x
Plasma biomarker sample [o]	x			x			x	x
Complete physical examination (including neurological systems) [g]				x			x	x
Limited physical examination [h]	x							x
Weight	x			x	x	x	x	x
MRI scan [i]	x [j]			x [j]			x [j]	x
CSF [k] and matching serum sampling (for participants enrolled based on CSF eligibility criteria only)				x			x [k]	
CDR	P&SP			P&SP		P&SP	P&SP	P&SP
ADAS-Cog13	P			P		P	P	P

Appendix 1: Schedule of Activities (cont.)
Table 4: Scenario 2 Only Week 104 to the End of Study: 510 mg Q2W (Additional 3-Month Extension)

Assessment/Procedure	Treatment Period			Final Safety and Efficacy Assessment	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
	Wk 104[a]	Wk 106-126[c]	Wk 127	Wk 128[a, b]	Wk 140	Wk 176		
Dose number	44	45-55						
Dose level in milligrams (mg)	510	510						
Verbal Fluency Task	P			P		P	P	P
Coding	P			P		P	P	P
ADCS-ADL	SP			SP		SP	SP	SP
FAQ	SP			SP		SP	SP	SP
MMSE	P			P		P	P	P
EQ-5D	SP			SP			SP	SP
QoL-AD	P&SP			P&SP			P&SP	P&SP
ZCI-AD	SP			SP			SP	SP
RUD-Lite	SP			SP			SP	SP
NPI-Q	SP			SP			SP	SP
C-SSRS BL/SLV	P			P			P	P
Vital signs [l]	x	x		x	x	x	x	x
Concomitant medications	x	x		x	x	x	x	x
Adverse events	x	x		x	x	x	x	x
Urine pregnancy test [m]	x	x		x	x		x	x
Study drug administration [d, n]	x	x						

ADAS-Cog13=Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL =Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR =Clinical Dementia Rating; CSF =cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D =EuroQol-Five Dimensions; FAQ =Functional Activities Questionnaire; FCSRT=Free and Cued Selective Reminding Test; MMSE =Mini-Mental State Examination; MRI =magnetic resonance imaging; NPI-Q =Neuropsychiatric Inventory–Questionnaire; OLE=open-label extension; PET =positron emission tomography; PK =pharmacokinetic; Q2W =every 2 weeks; QoL-AD =Quality of Life–Alzheimer's Disease; RBR =Research Biosample Repository; RUD-Lite =Resource Utilization in Dementia–Lite; SC =subcutaneous; Unsched =unscheduled; Wk =week; ZCI-AD =Zarit Caregiver Interview–Alzheimer's Disease.

Appendix 1: Schedule of Activities (cont.)
Table 4: Scenario 2 Only Week 104 to the End of Study: 510 mg Q2W (Additional 3-Month Extension)

B =before study drug administration; P =participant completion; P&SP=participant and study partner completion; SP=study partner.

Notes: The visit window is ±3 days for dosing days and +3 days for Week 127 non-dosing days. For Q2W injections, the recommendation is not to administer more than 1020 mg (i.e., 2 times 510 mg Q2W) within 28 days. Participants should return to initial planned schedule per randomization for subsequent visits.

SoA from Week –12 to Week 103 for scenario 2 is described in Appendix 1, Table 1 and Table 2.

[a] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vitals, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.

[b] Transition to OLE study for participants who are eligible to participate.

[c] Visit suitable for home administration of gantenerumab.

[d] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria

[e] Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). At Week 104 and Week 128, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[f] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

[g] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

[h] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[i] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[j] Includes resting-state functional MRI and DTI outcome measures, where available.

[k] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For participants enrolling based on CSF eligibility criteria, CSF and matching serum samples are optional at Week 76; lumbar puncture does not have to be performed the day of Week 76 or Week 128 visit, but should be performed in a reasonable time around these visits; the need of CSF collection at early termination visit *should be determined on a case-by-case basis based on the participant's condition and the time since last lumbar puncture and advice from* the Medical Monitor may be sought.

[l] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[m] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[n] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by subcutaneous injection (full details are provided in the pharmacy manual). Participants should be observed for about 1 hour after dosing. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[o] A plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria

Appendix 1
Schedule of Activities (cont.)

Table 5: Schedule of Activities (OLE Day 1 to Week 22: Dose Escalation with Q2W Administration)

Assessment/Procedure	Open-Label Extension Treatment Period													OLE Early Term Visit [m]	OLE UV
	OLE Day 1	OLE Day 4	OLE Wk 2	OLE Wk 4	OLE Wk 6	OLE Wk 8	OLE Wk 10	OLE Wk 12	OLE Wk 14	OLE Wk 16	OLE Wk 18	OLE Wk 20	OLE Wk 22		
Dose number	1[a]		2	3	4	5	6	7	8	9[b]	10[b]	11[b]	12[b]		
Dose level in milligrams (mg) for participants previously on placebo	120			120		120		255		255		255			
Dose level in milligrams (mg) for participants previously on active	510		510	510	510	510	510	510	510	510	510	510	510		
Informed consent(s)	x														
Review of inclusion and exclusion criteria	x														
Weight														x	x
12-Lead electrocardiogram								B						x	x
PK Plasma Sample [c]	x	x												x	x
ADA sample	x													x	x
Serum chemistry [d] and hematology [e]														x	x

Appendix 1: Schedule of Activities (cont.)
Table 5: Schedule of Activities (OLE Day 1 to Week 22: Dose Escalation with Q2W Administration) (cont.)

Assessment/Procedure	Open-Label Extension Treatment Period													OLE Early Term Visit [m]	OLE UV
	OLE Day 1	OLE Day 4	OLE Wk 2	OLE Wk 4	OLE Wk 6	OLE Wk 8	OLE Wk 10	OLE Wk 12	OLE Wk 14	OLE Wk 16	OLE Wk 18	OLE Wk 20	OLE Wk 22		
Dose number	1[a]		2	3	4	5	6	7	8	9[b]	10[b]	11[b]	12[b]		
Dose level in milligrams (mg) for participants previously on placebo	120			120		120		255		255		255			
Dose level in milligrams (mg) for participants previously on active	510		510	510	510	510	510	510	510	510	510	510	510		
Plasma biomarker sample [l]														x	x
Complete physical examination (includes neurological systems) [f]														x	x
Limited physical examination [g]															x
MRI scan [h]								B						x [n]	x
CDR														P&SP	P&SP
ADAS-Cog 13														P	P
MMSE														P	P
Verbal Fluency Test														P	P
Coding														P	P
ADCS-ADL														SP	SP
FAQ														SP	SP
EQ-5D														SP	SP
QoL-AD														P&SP	P&SP
ZCI-AD														SP	SP

Appendix 1: Schedule of Activities (cont.)
Table 5: Schedule of Activities (OLE Day 1 to Week 22: Dose Escalation with Q2W Administration) (cont.)

Assessment/Procedure	Open-Label Extension Treatment Period													OLE Early Term Visit [m]	OLE UV
	OLE Day 1	OLE Day 4	OLE Wk 2	OLE Wk 4	OLE Wk 6	OLE Wk 8	OLE Wk 10	OLE Wk 12	OLE Wk 14	OLE Wk 16	OLE Wk 18	OLE Wk 20	OLE Wk 22		
Dose number	1[a]		2	3	4	5	6	7	8	9 [b]	10 [b]	11 [b]	12 [b]		
Dose level in milligrams (mg) for participants previously on placebo	120			120		120		255		255		255			
Dose level in milligrams (mg) for participants previously on active	510		510	510	510	510	510	510	510	510	510	510	510		
RUD-Lite														SP	SP
NPI-Q														SP	SP
C-SSRS/SLV														P	P
CSF and matching serum sampling (for participants enrolled based on CSF eligibility criteria in double-blind part only)														x [o]	
Vital Signs [i]	B	x	B	B	B	B	B	B	B	B	B	B	B	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [i]	B		B	B	B	B	B	B	B	B	B	B	B	x	x
Study drug administration [c, k]	x		x	x	x	x	x	x	x	x	x	x	x		

ADAS-Cog13= Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR = Clinical Dementia Rating; CSF = cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; FCSRT= Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; OLE=open-label extension; PET = positron emission

tomography; PK = pharmacokinetic; Q2W = every 2 weeks; QoL-AD = Quality of Life–Alzheimer's Disease; RBR = Research Biosample Repository; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; UV = unscheduled visit; Wk = week; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

B = before study drug administration; P = participant completion; P&SP= participant and study partner completion; SP=study partner.

Notes: The visit window is ± 3 days for dosing days and +3 days for OLE non-dosing Day 4. Participants should return to initial planned schedule per randomization for subsequent visits.

[a] OLE Day 1 dosing should take place approximately 2 weeks after final efficacy visit has been completed.

[b] Visit suitable for home administration of gantenerumab.

[c] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria

[d] Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). At early termination, hemoglobin A1C, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[e] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

[f] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

[g] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[h] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[i] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[j] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[k] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by subcutaneous injection (full details are provided in the pharmacy manual). Participants should be observed for up to 2 hours after dosing. After the 8th injection visit, this observation time may be reduced to 1 hour. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[l] A plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria

[m] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vitals, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater or even the participant cannot perform these assessments as per schedule of activities they may be performed up to 4 weeks out of window.

[n] Includes resting-state functional MRI and DTI outcome measures, where available.

[o] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For patients enrolling based on CSF eligibility criteria, the need of CSF collection at early termination visit during OLE *should be determined* on a case-by-case basis *based on the participant's condition and the time since last lumbar puncture and advice from* the Medical Monitor may be sought.

Appendix 1
Schedule of Activities (cont.)

Table 6: Schedule of Activities (OLE Week 24 to Week 35: Dose Escalation with Q2W Administration)

Assessment/Procedure	Open-Label Extension Treatment Period							Follow-up Period for Participants Not Enrolling in Study WN42171		OLE Early Term Visit [a]	OLE Unsched Visit
	OLE Wk 24	OLE Wk 26	OLE Wk 28	OLE Wk 30	OLE Wk 32	OLE Wk 34	OLE Wk 35	OLE Follow Up 1	OLE Follow Up 2		
Dose number	13 [a]	14 [b]	15 [b]	16 [b]	17 [b]	18 [b]					
Dose level in milligrams (mg) for participants previously on placebo	510		510		510						
Dose level in milligrams (mg) for participants previously on active	510	510	510	510	510	510					
Informed consent(s)											
Review of inclusion and exclusion criteria											
Weight	x							x	x	x	x
12-Lead electrocardiogram	x							x		x	x
PK plasma sample [c]	x							x	x	*x*	*x*
ADA sample	x							x	x	x	x
Serum chemistry [d] and hematology [e]	x							x	x	x	x
Plasma biomarker sample [n]	x									x	x
Complete physical examination (includes neurological systems) [f]										x	x
Limited physical examination [g]	x										x

Appendix 1: Schedule of Activities (cont.)
Table 6: Schedule of Activities (OLE Week 24 to Week 35: Dose Escalation with Q2W Administration) (cont.)

Assessment/Procedure	Open-Label Extension Treatment Period							Follow-up Period for Participants Not Enrolling in Study WN42171		OLE Early Term Visit [a]	OLE Unsched Visit
	OLE Wk 24	OLE Wk 26	OLE Wk 28	OLE Wk 30	OLE Wk 32	OLE Wk 34	OLE Wk 35	OLE Follow Up 1	OLE Follow Up 2		
Dose number	13 [a]	14 [b]	15 [b]	16 [b]	17 [b]	18 [b]					
Dose level in milligrams (mg) for participants previously on placebo	510		510		510						
Dose level in milligrams (mg) for participants previously on active	510	510	510	510	510	510					
MRI scan [h]	B						x			x[i]	x
CDR	P&SP								P&SP	P&SP	P&SP
ADAS-Cog 13	P								P	P	P
MMSE	P								P	P	P
Verbal Fluency Test	P								P	P	P
Coding	P								P	P	P
ADCS-ADL	SP								SP	SP	SP
FAQ	SP								SP	SP	SP
EQ-5D	SP								SP	SP	SP
QoL-AD	P&SP								P&SP	P&SP	P&SP
ZCI-AD	SP								SP	SP	SP
RUD-Lite	SP								SP	SP	SP
NPI-Q	SP								SP	SP	SP
C-SSRS/SLV	P								P	P	P

Appendix 1: Schedule of Activities (cont.)
Table 6: Schedule of Activities (OLE Week 24 to Week 35: Dose Escalation with Q2W Administration) (cont.)

Assessment/Procedure	Open-Label Extension Treatment Period							Follow-up Period for Participants Not Enrolling in Study WN42171		OLE Early Term Visit [a]	OLE Unsched Visit
	OLE Wk 24	OLE Wk 26	OLE Wk 28	OLE Wk 30	OLE Wk 32	OLE Wk 34	OLE Wk 35	OLE Follow Up 1	OLE Follow Up 2		
Dose number	13 [a]	14 [b]	15 [b]	16 [b]	17 [b]	18 [b]					
Dose level in milligrams (mg) for participants previously on placebo	510		510		510						
Dose level in milligrams (mg) for participants previously on active	510	510	510	510	510	510					
CSF and matching serum sampling (for participants enrolled based on CSF eligibility criteria in double-blind part only)										x [j]	
Vital signs [k]	B	B	B	B	B	B		x	x	x	x
Concomitant medications	x	x	x	x	x	x		x	x	x	x
Adverse events	x	x	x	x	x	x		x	x	x	x
Urine pregnancy test [l]	B	B	B	B	B	B		x		x	x
Study drug administration [c, m]	x	x	x	x	x	x					

ADAS-Cog13= Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR = Clinical Dementia Rating; CSF = cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; FCSRT= Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; OLE=open-label extension; PET = positron emission tomography; PK = pharmacokinetic; Q2W = every 2 weeks; QoL-AD = Quality of Life–Alzheimer's Disease; RBR = Research Biosample Repository; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; Unsched = unscheduled; Wk = week; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

B = before study drug administration; P = participant completion; P&SP= participant and study partner completion; SP=study partner.

Appendix 1: Schedule of Activities (cont.)
Table 6: Schedule of Activities (OLE Week 24 to Week 35: Dose Escalation with Q2W Administration) (cont.)

Notes: The visit window is ± 3 days for dosing days and +3 days for OLE non-dosing Day 4. Participants should return to initial planned schedule per randomization for subsequent visits.

[a] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vitals, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater or even the participant cannot perform these assessments as per schedule of activities they may be performed up to 4 weeks out of window.

[b] Visit suitable for home administration of gantenerumab.

[c] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

[d] Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). At early termination, hemoglobin A1C, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[e] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

[f] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

[g] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[h] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[i] Includes resting-state functional MRI and DTI outcome measures, where available.

[j] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For participants enrolling based on CSF eligibility criteria, the need of CSF collection at early termination visit during OLE *should be determined* on a case-by-case basis *based on the participant's condition and the time since last lumbar puncture and advice from* the Medical Monitor may be sought.

[k] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[l] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[m] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by subcutaneous injection (full details are provided in the pharmacy manual). Participants should be observed for up to 2 hours after dosing. After the 8th injection visit, this observation time may be reduced to 1 hour. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[n] A plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

Appendix 2
National Institute on Aging/Alzheimer's Association Criteria for Mild Alzheimer's Disease

NIA/AA Category	Description
Probable dementia: core clinical criteria Meets criteria for dementia described earlier in the text, and, in addition, has the following characteristics:	A. Insidious onset: Symptoms have a gradual onset over months to years, not sudden over hours or days B. Clear-cut history of worsening of cognition by report or observation; and C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories: 1. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text. 2. Non-amnestic presentations • Language presentation: The most prominent deficits are in word finding, but deficits in other cognitive domains should be present. • Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present. • Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present. D. The diagnosis of probable AD dementia should not be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or non-fluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

Appendix 2: National Institute on Aging/Alzheimer's Association Criteria for Mild Alzheimer's Disease (cont.)

NIA/AA Category	Description
Probable AD dementia with increased level of certainty	**Probable AD dementia with documented decline** In persons who meet the core clinical criteria for probable AD dementia, documented cognitive decline increases the certainty that the condition represents an active, evolving pathologic process, but it does not specifically increase the certainty that the process is that of AD pathophysiology. Probable AD dementia with documented decline is defined as follows: evidence of progressive cognitive decline on subsequent evaluations based on information from informants and cognitive testing in the context of either formal neuropsychological evaluation or standardized mental status examinations. **Probable AD dementia in a carrier of a causative AD genetic mutation** In persons who meet the core clinical criteria for probable AD dementia, evidence of a causative genetic mutation (in APP, PSEN1, or PSEN2) increases the certainty that the condition is caused by AD pathology. The working group noted that carriage of the ε4 allele of the *APOE* gene was not sufficiently specific to be considered in this category.
Probable AD dementia with evidence of the AD pathophysiological process	AD dementia is part of a continuum of clinical and biological phenomena. AD dementia is fundamentally a clinical diagnosis. To make a diagnosis of AD dementia with biomarker support, the core clinical diagnosis of AD dementia must first be satisfied. Relevant biomarkers include amyloid-β (CSF or PET) and tau (CSF or PET).

AD = Alzheimer's disease; *APOE* = apolipoprotein E; CSF = cerebral spinal fluid; NIA/AA = National Institute on Aging/Alzheimer's Association; PET = positron emission tomography.

REFERENCE

McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:263–9.

Appendix 3
National Institute on Aging/Alzheimer's Association Criteria for Prodromal Alzheimer's Disease (Mild Cognitive Impairment due to Alzheimer's Disease)

NIA/AA Category	Clinical and Cognitive Criteria
Clinical criteria	• Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time) • Objective evidence of impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains) • Preservation of independence in functional abilities • Not demented
Etiology of MCI consistent with AD pathophysiological process	• Rule out vascular, traumatic, medical causes of cognitive decline, when possible • Provide evidence of longitudinal decline in cognition, when feasible • Report history consistent with AD genetic factors, when relevant
Prodromal AD dementia with evidence of the AD pathophysiological process	Prodromal AD is part of a continuum of clinical and biological phenomena. Prodromal AD is fundamentally a clinical diagnosis. To make a diagnosis of prodromal AD with biomarker support, the core clinical diagnosis of prodromal AD must first be satisfied. Relevant biomarkers include amyloid-β (CSF or PET) and tau (CSF or PET).

AD = Alzheimer's disease; CSF = cerebral spinal fluid; MCI = mild cognitive impairment; NIA/AA = National Institute on Aging/Alzheimer's Association; PET = positron emission tomography.

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Albert MS, DeKosky ST, Dickson B, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270–9.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data

The population pharmacokinetic positron emission tomography (PK-PET) response analysis of the gantenerumab Phase III Study WN25203 data and aducanumab Phase Ib PET study model was built using pooled information from the gantenerumab Phase III study WN25203 and the aducanumab Phase Ib PRIME study. Details about how this population analysis was conducted and evaluated are provided herein.

1. MATERIALS AND METHODS

1.1 MODELING HYPOTHESIS

Based on the high degree of similarity between gantenerumab and aducanumab, it was assumed that both compounds share the same PK properties in terms of disposition, metabolism, elimination, and the same relationship between in serum concentrations and reduction in standardized uptake value ratio (SUVr) amyloid PET.

It was also assumed that the SUVr data from aducanumab and gantenerumab could be pooled given that they were derived using the same whole cerebellum reference region and that the sensorimotor region used only in the composite SUVr of aducanumab was having little effect on the SUVr values.

1.2 PHARMACOKINETIC AND PHARMCODYNAMIC DATA

A PK-pharmacodynamic (PD) dataset for PET model was built using information from the Phase III gantenerumab study (WN25203) together with information from Phase Ib aducanumab trial (PRIME).

2.2.1 Gantenerumab PK and PET Data

2.2.1.1 PK Information

Each patient participating in Study WN25203 provided samples for measurement of their PK serum concentrations at the following scheduled timepoints: Weeks 1, 8, 20, 44, 53, 68, 100, and 101.

The PK data from Study WN25203 were analysed using a population PK model that was previously developed on the basis of Phase I studies.

The Phase I PK database comprised data from 235 patients and healthy volunteers for a total of 4082 PK observations. It contained data from both IV and SC administration, single and multiple repeated doses administered every 4 weeks (Q4W), with dose values ranging for the repeated dose administrations from 6 mg to 200 mg for the IV, 105 and 225 mg for the SC, and up to 300 mg SC and 400 mg IV when administered

once. A two-compartment model with a 0 order followed by first-order absorption best described the Phase I data. Population parameter values are reported in Table 1.

Table 1 Population PK Parameters Estimated from Phase I Study Data

Parameter	Mean	RSE%	BSV%	RSE%
CL (L/day)	0.336	3.20%	26.1%	6.9%
V2 (L)	3.52	5.60%	31.3%	18.5%
Q (L/day)	0.869	9.50%	55.5%	10.6%
V3 (L)	6.38	4.10%	24.9%	10%
KA (/day)	0.22	8.90%	52.2%	21.1%
D1 (/day)	0.0821	7.10%	96.6%	8.9%
F1 (–)	0.494	3.90%	42.8%	10.5%
PROP.ERR	0.196	5.40%		
ADD.ERR (μg/mL)	0.0121	21.70%		

ADD_ERR = additional error; CL=clearance; D1 = zero order rate constant; F1 = absolute bioavailability; KA = absorption rate constant; KeO = rate constant for drug transfer from serum to effect compartment; PK = pharmacokinetic; POW = power; PROP_ERR = proportional error; Q = intercompartmental clearance; RSE = relative standard error; SLOP = slope; V2 = central compartment; V3 = peripheral volume 3.

The population PK model was used to perform an empirical Bayesian analysis in non-linear mixed-effects model (NONMEM) of the PK data collected from Study WN25203 and to derive for each patient the individual PK parameters, as well as an estimation of the individual average concentrations over the period of observation.

2.2.1.2 PET Information

Among the 799 patients enrolled in Study WN25203, 114 patients participated in the amyloid PET substudy (using the AV-45 ligand). Scans were performed at baseline, Weeks 20, 60, and 100. For patients entering the 2-year, double-blinded portion of the trial (Part 2), another scan was obtained at Week 156.

PET data up to Week 100 (inclusive) were considered for the PK-PD modeling investigations, and the PET database comprised a total of 348 SUVr observations determined using the whole cerebellum as the reference region.

2.2.2 Aducanumab PK and PET PD Data

Aducanumab PK and PET data were extracted from a poster (n°ADPD5–2113) and from slides that were presented at the 12th International Congress on Alzheimer's Disease and Parkinson's Disease (ADPD) in March 2015 in Nice, France.

The aducanumab data were collected in the Phase Ib, randomized, double-blind, placebo-controlled study (PRIME) in patients with prodromal or mild Alzheimer's

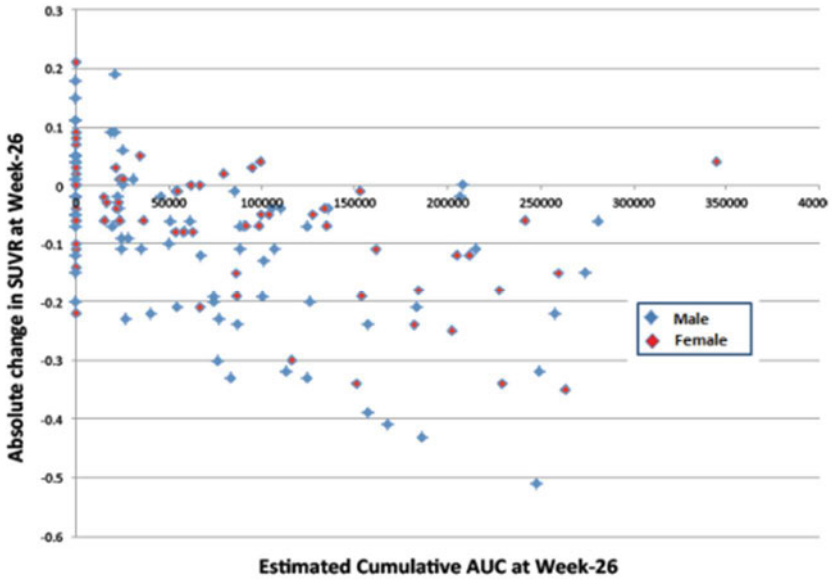
disease. The study design involved a parallel-group design, with a 54-week treatment period. Patients received 14 IV infusions of aducanumab Q4W; four dose groups were evaluated, including the placebo group, and included the 1-mg/kg, 3-mg/kg, 6-mg/kg, and 10-mg/kg dose groups, respectively. SUVr measurements were performed at baseline, Week 26, and Week 54 and were determined using the whole cerebellum as the reference region.

The following figures were used from the aducanumab poster and slides:

- A figure displaying the individual absolute change in SUVr at Week 26 in function of the individual cumulative area under the concentration-time curve (AUC) at Week 26 (see Figure 1)
- A table presenting the time course of the mean SUVr up to Week 54 by dose group (see Table 2)
- A figure displaying the relationship between the individual cumulative AUC at Week 26 and the four doses investigated in the PRIME study (see Figure 2)

The individual data, as depicted in Figure 1, were extracted and a database of 123 patients with their respective cumulative AUC values at Week 26 and the absolute change from baseline in SUVr. The mean data from Figure 2 were used to extrapolate the individual aducanumab PET data at Weeks 26 to 54 and, also, to assign a mean SUVr baseline value to each aducanumab dose group. In addition, the data from Figure 2 were used to determine from which dose group the individual cumulative AUC values at Week 26 from Figure 1 were most likely derived.

Figure 1 Individual Absolute Change in SUVr Observed in Aducanumab Data at Week 26 with Respect to Cumulative Exposure



AUC = area under the concentration–time curve; SUVr = standardized uptake value ratio.
Source: Hang et al. 2015.

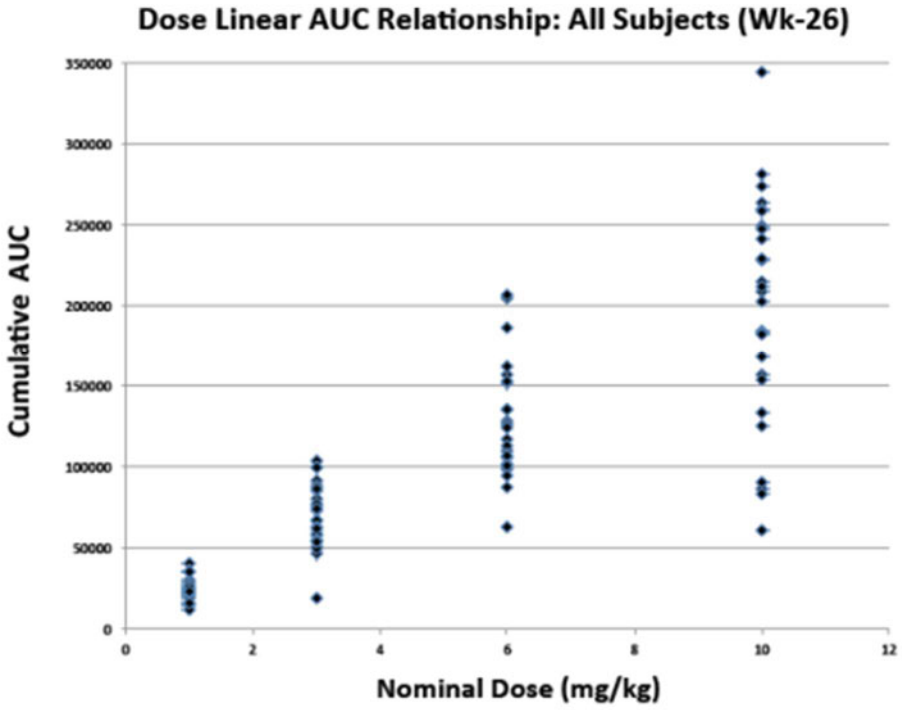
Table 2 Mean Composite PET SUVr Data Observed in the Aducanumab Phase Ib Trial (PRIME) per Dose Group, Using the Whole Cerebellum as Reference Region

	Observed Mean Composite SUVr		
Dose Group	Baseline	Week 26	Week 54
Placebo	1.45	1.42	1.42
1 mg/kg	1.45	1.395	1.346
3 mg/kg	1.471	1.365	1.3
6 mg/kg	1.44	1.288	–
10 mg/kg	1.434	1.223	1.152

SUVr = standardized uptake value ratio.

Source: Data derived from presented slide at ADPD conference.

Figure 2 Individual Dose–Exposure Relationship Observed in the Aducanumab Phase Ib Trial (PRIME)



AUC = area under the concentration–time curve.

Note: Subjects demonstrating low cumulative aducumab exposures were primarily due to missed doses.

Source: Hang et al. 2015.

2.3 POPULATION PK-PD METHODS

2.3.1 Structural PK-PD Model

Several structural PK-PD models were evaluated to best describe the link between exposure and SUVr PET. The tested models included a direct relationship, as well as an indirect relationship, using an effect-compartment model to take into account a time delay for the concentrations in serum to reach the effect site.

Furthermore, several types of drug effect were tested, including a linear model, a power model, an E_{max} model, and a sigmoid E_{max} model.

No placebo models were evaluated because no specific placebo response was noticed during the observations period.

An additive error model was used for the residual variability. The baseline PET SUVr values were used as covariate in the model, but with an associated residual error of the same magnitude of the additive error model.

Inter-individual variability was tested on the PK-PD parameters by assuming a log-normal distribution.

2.3.2 PK-PD Model Selection and Evaluation

Models were selected by means of visual inspection of basic goodness-of-fits plots, including, but not limited to, plots of the observed data versus population (PRED) and individual predictions (IPRED), plots of individual weighted residuals (IWRES) versus IPRED, and the distribution of weighted residuals (WRES) over time. Relative standard errors (RSE) of the parameters were also compared to measure parameter precision. The NONMEM objective function value (OFV) was used to discriminate between nested models. This discrimination was based on a significance level of 0.05, which corresponds to a decrease of >3.84 in OFV (for one degree of freedom), as the difference in OFV is approximately χ^2 distributed.

Additionally, visual predictive check (VPC) was performed to test the model appropriateness by means of computing confidence intervals (CIs) derived from 1000 simulated data sets, using the final model and final parameter estimates, for each statistic (i.e., the median, the 5th and the 95th percentiles). Several VPCs were performed, either to test the appropriateness of the model when predicting the gantenerumab and aducanumab pooled dataset or to focus separately on the two compounds datasets. Furthermore, they were produced per level of exposure as well as per level of doses.

2.3.3 Computer Programs

The analyses were performed in NONMEM Version 7.2, using FOCE INTERACTION (Beal and Sheiner 1992). Graphics and NONMEM datasets were created using Version 3.1.2 and/or the SAS system for Windows, Version 9.3.

2.4 COVARIATE ANALYSIS

Only limited covariate information was available from the aducanumab data, and an exploratory graphical analysis of individual post-hoc parameters was conducted only for the following covariates: PET baseline values, compound type, sex, and dose.

3. RESULTS

3.1 DATA

The final PK-PD dataset combining aducanumab and gantenerumab data included 237 patients with a total of 693 PET SUVr observations.

3.2 POPULATION EXPOSURE SUVr PET MODEL

The relationship between exposure and the PET SUVr reduction time course was best described by using a power model combined with an effect compartment to account for the delay between exposure and PET response. The model equations are as follows:

$$\mathrm{PET}(\mathrm{time}) = \mathrm{Base} * \left(1 - \mathrm{SLOP} * (\mathrm{Conc_E}(\mathrm{time}))^{\mathrm{POW}}\right)$$

with $$\frac{\mathrm{dConc_E}(\mathrm{time})}{\mathrm{dtime}} = \mathrm{Ke0} * (\mathrm{Conc}(\mathrm{time}) - \mathrm{Conc_E}(\mathrm{time}))$$

with Base the individual PET SUVr baseline value, $\mathrm{Conc_E}$ the predicted concentration at effect site, Conc the predicted concentration in serum, $\mathrm{Ke0}$ the rate constant for drug transfer from serum to effect compartment, and SLOP and POW the parameters driving the drug effect.

Parameter values are reported in Table 3.

Table 3 Estimated Population PK-PD Parameters

Parameter	Mean (RSE%)	Value Inter-Individual Variability (RSE%)
Ke0 (Day $^{-1}$)	1.74×10^{-3} (38%)	127.3% (14%)
Equilibration half-life (weeks)	57	
SLOP	0.019 (33%)	—
POW (–)	0.716 (11%)	—
ADD_ERR	0.0659 (5%)	

ADD_ERR = additional error; KeO = rate constant for drug transfer from serum to the effect compartment; PD = pharmacodynamic; PK = pharmacokinetic; POW = power; RSE = relative standard error; SLOP = slope.

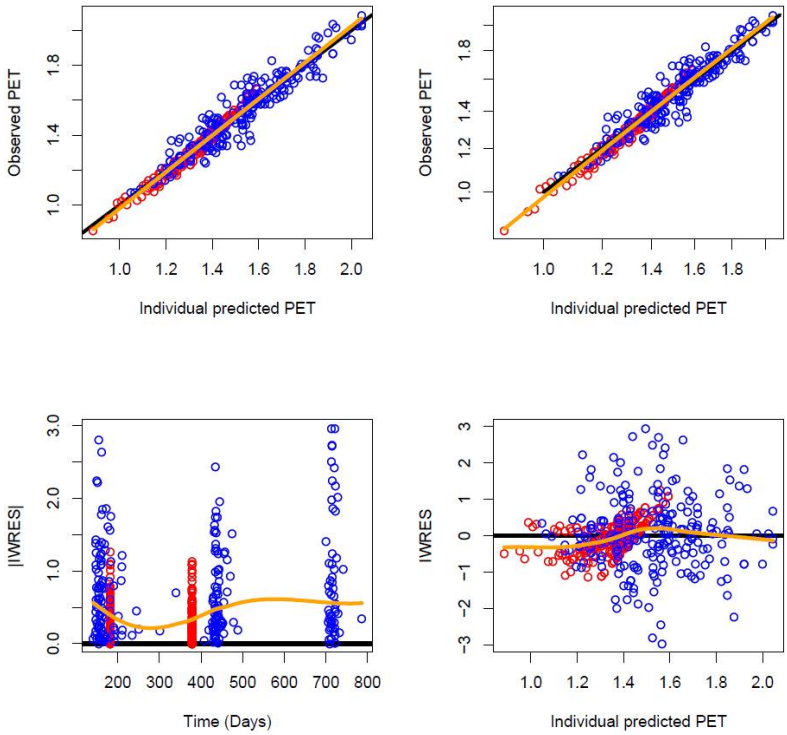
Inspection of the goodness-of-fit plots reported in Figure 3 shows that the final PK-PD model describes the data adequately without obvious bias in the population or individual predicted PET values. The VPCs are shown in Figures 5–7. The shaded areas indicate the 90% CIs (i.e., 5th and 95th percentiles) computed from simulations. The median and

the 5th and 95th percentiles of the observed PK profiles are contained in their respective CIs, indicating that the final PK-PD model captures both the central tendency and the between-subject variability of both gantenerumab and aducanumab pharmacodynamics in the target populations of patients with prodromal and mild Alzheimer's disease.

3.3 COVARIATE ANALYSIS

The exploratory graphical covariate analysis is reported on Figure 4. Although a small trend between PET baseline values and estimated individual Ke0, this graphical analysis did not reveal any relevant covariate relationships that would require further investigation.

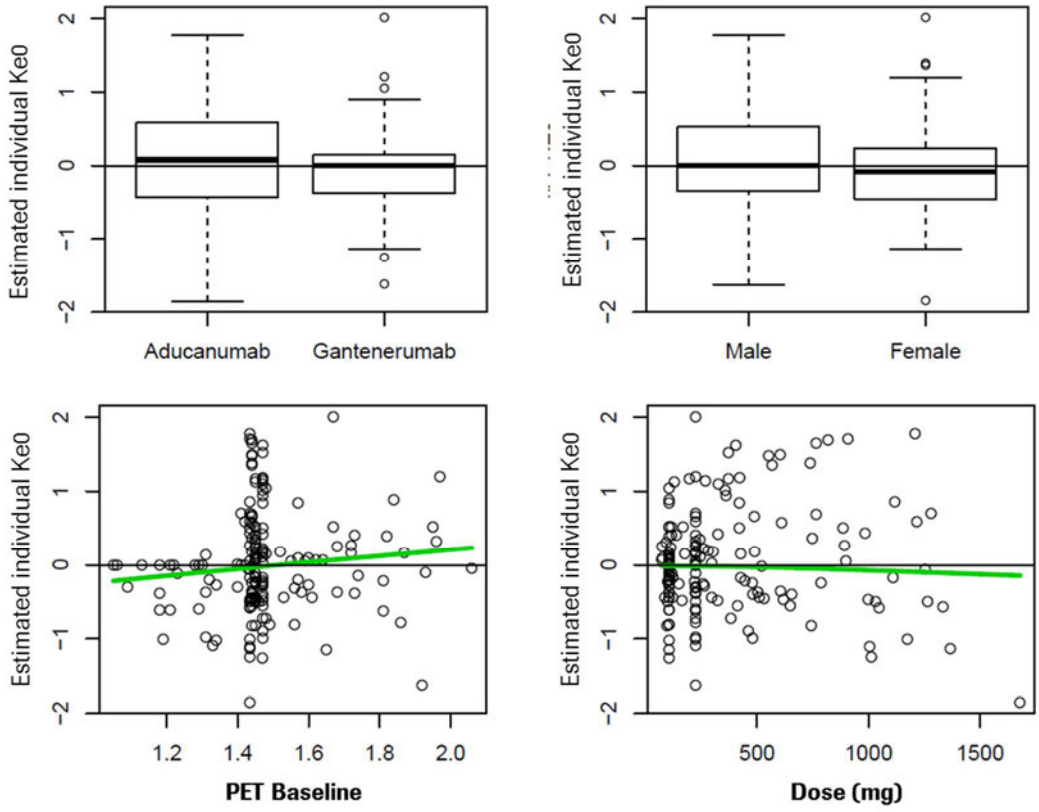
Figure 3 Goodness-of-Fit Plots for the Final PK-PD Model



IWES = individual weighted residual value; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

Note: The red dots represent the aducanumab compound, and blue dots represent gantenerumab compound. The orange lines correspond to a smoothing of the data.

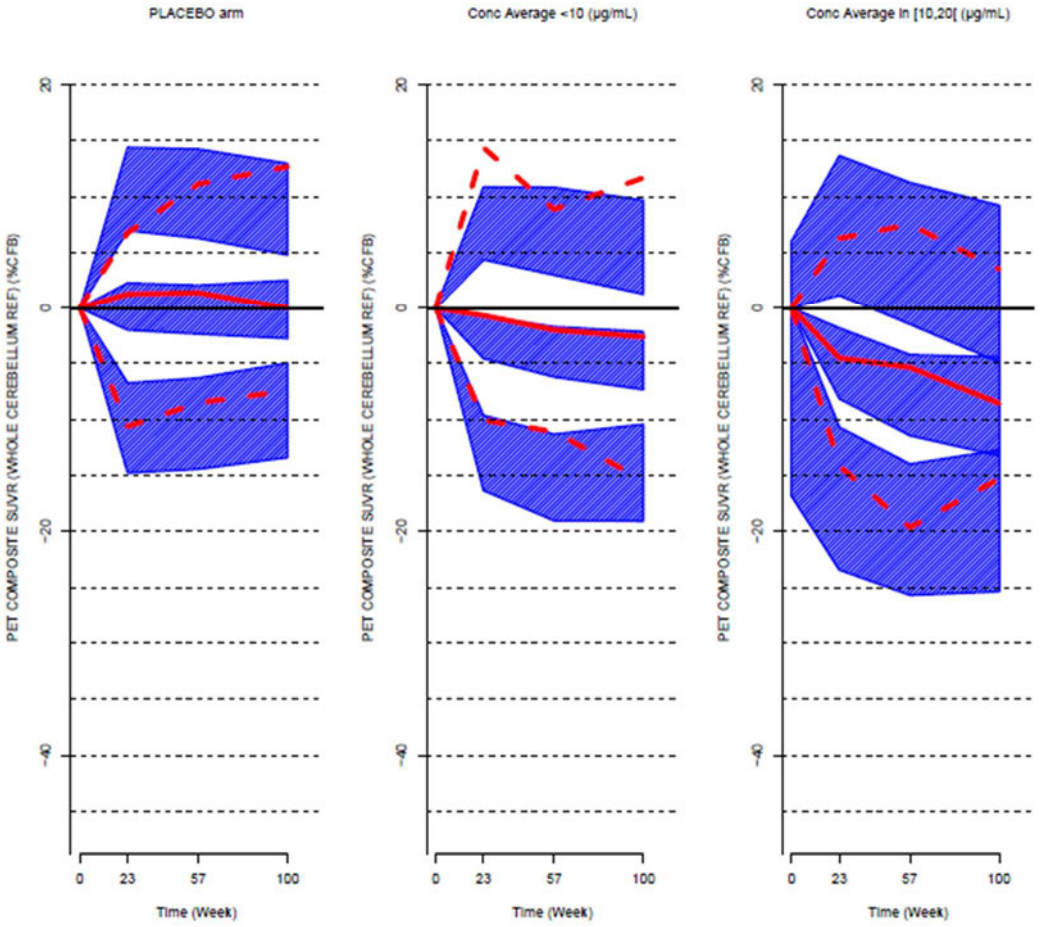
Figure 4 Exploratory Analysis of Covariates (by Compound Type, Sex, PET Baseline Value, and Dose [in milligrams] Value with Respect to Estimated Individual Ke0)



KeO = rate constant for drug transfer from serum to the effect compartment; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

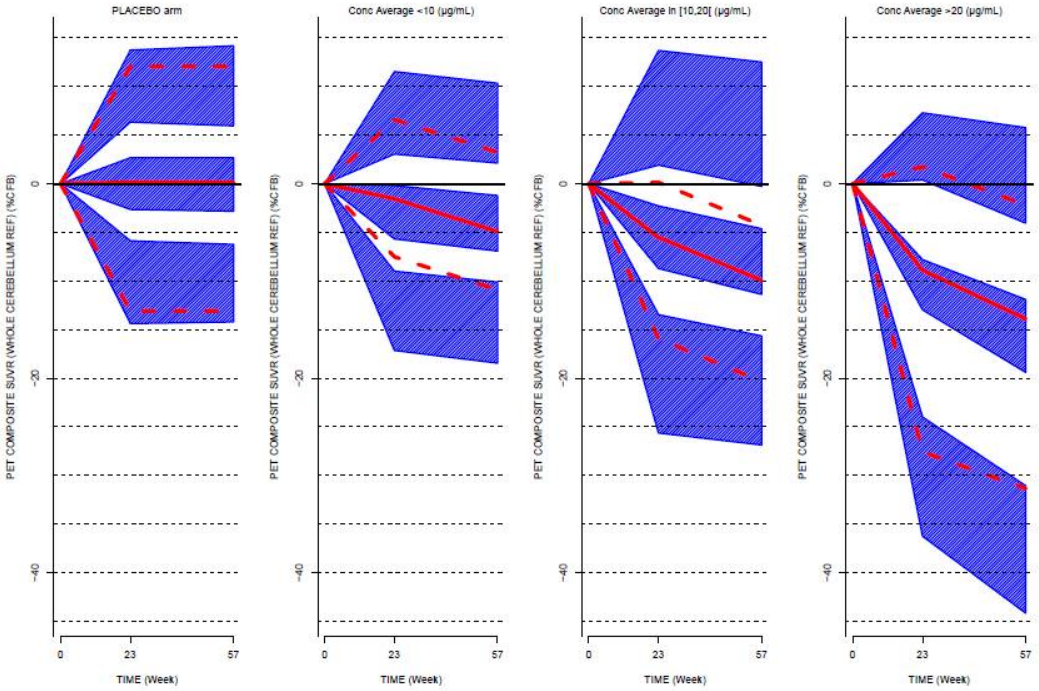
Note: Dose was investigated in milligrams, using a mean weight of 70 kg for doses the aducanumab PRIME study. The green line corresponds to a smoothing of the data.

Figure 5 Visual Predictive Check of the PET Model by Category of Serum Concentration Exposure for the Gantenerumab WN25203 Alone



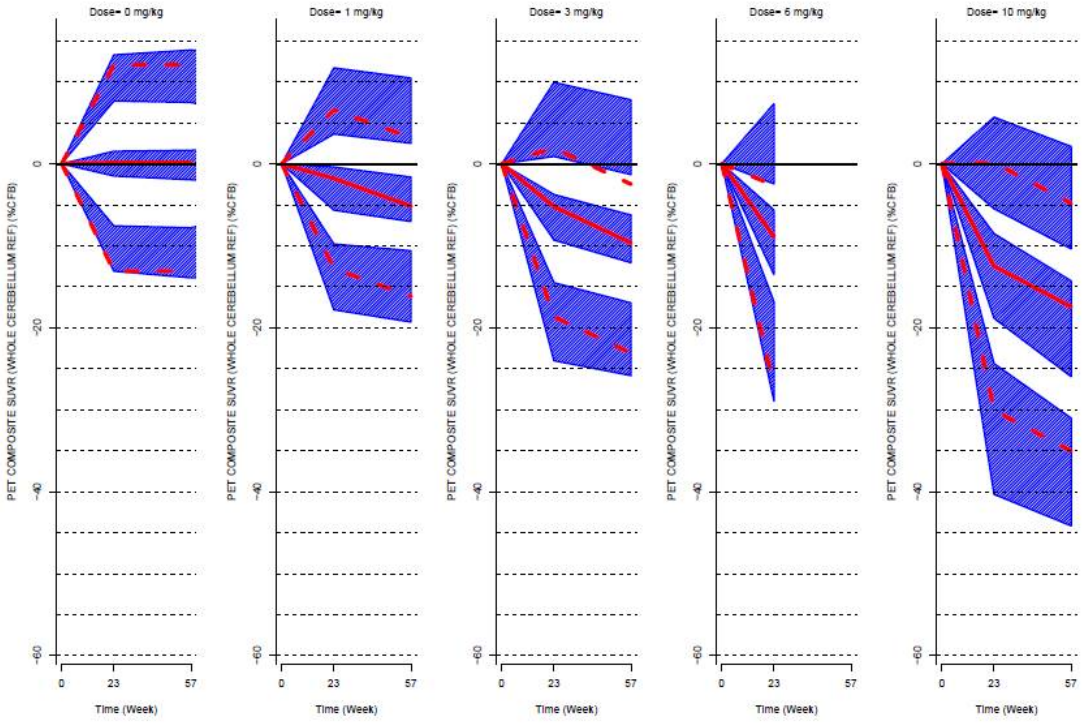
CFB = change from baseline; Conc = concentration; KeO = rate constant for drug transfer from serum to the effect compartment; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

Figure 6 Visual Predictive Check of the PET Model Per Category of Serum Concentration Exposure for the Aducanumab PRIME Study Alone



KeO = rate constant for drug transfer from serum to the effect compartment; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

Figure 7 Visual Predictive Check of the PET Model by Category of Expected Dose Group for the Aducanumab PRIME Trial Alone



KeO = rate constant for drug transfer from serum to the effect compartment; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

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Hang Y, Chiao P, Sevigny J, et al. Pharmacokinetic and pharmacodynamic (PK-PD) assessment and covariate analysis of aducanumab (BIIB037) in a randomized, double-blind, placebo-controlled, Phase 1b study (PRIME) in subjects with prodromal or mild Alzheimer's disease. 12th International Congress on Alzheimer's and Parkinson's Disease. Poster presentation. March 2015. Nice, France.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model

1. BACKGROUND

Hutmacher et al. (2013) presented a pharmacodynamic (PD) model for bapineuzumab addressing the first occurrence of amyloid-related imaging abnormalities, or ARIAs, of "vasogenic edema" (ARIA-E) events. Patients received constant dose regimens of 0.5, 1, and 2 mg/kg given every 13 weeks over 1.5 years. A total of 2435 patients with 243 ARIA-E events were analysed. As shown below, a log hazard model was developed that included three elements:

- A baseline value (I_{BS}) reflecting a constant ARIA-E hazard for apolipoprotein E allele ε4 (*APOE* ε4) gene carriers and non-carriers, respectively.
- Plasma drug concentrations (c) of bapineuzumab modulating the ARIA-E hazard through the maximum effect (E_{max}) of drug and 50% of the effective concentration (EC_{50}) parameters.
- A time component continuously suppressing the ARIA-E hazard by the time (t) since first dosing. ET_{50} and γ modulated this effect.

$$\log h(t) = I_{BS} + \frac{E_{\max} \cdot c(t)}{c(t) + EC_{50}} \cdot \frac{ET_{50}^{\gamma}}{ET_{50}^{\gamma} + t^{\gamma}}$$

Because no model parameters were reported in Hutmacher et al. 2013, the parameters were derived from predicted time-concentration and time-hazard curves presented in Hutmacher et al. 2013 after digitizing the respective graphs for 0.5 mg/kg in *APOE ε4* carriers. I_{BS} parameters were obtained from the graphs directly, whereas the other parameters were calculated from the digitized data using MATLAB (or matrix laboratory) and maximum likelihood estimation. Parameter values are shown in Table 1.

Table 1 Estimated Pharmacodynamic Parameters for Bapineuzumab

I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (μg/mL)
8.7E-6 (non-carrier) 3.55E-5 (carrier)	323.441	2.146	6.891	2.64

2. ARIA EVENTS UNDER CONSTANT DOSING REGIMENS

The above model was applied to the double-blind phase of Study WN25203, in which patients received constant dose regimens of 105 and 225 mg of gantenerumab. Owing to paucity of ARIA event data and the assumed independence between time and study drug–related hazard model parameters, I_{BS}, ET_{50}, and γ were fixed to the bapineuzumab values, and only E_{max} and EC_{50} were estimated.

The concentration-time course for gantenerumab in Study WN25203 was derived from a population PK model previously developed for Phase I studies. It covers both intravenous (IV) and subcutaneous (SC) administration, as well as single and multiple repeated doses every 4 weeks, with a range of dose values for the repeated dose administrations from 6 mg to 200 mg for IV administration, 105 mg and 225 mg for SC administration, and up to 300 mg SC and 400 mg for IV administration when given only once. The parameters for this model are presented in Table 2.

Table 2 Pharmacokinetic Parameters for Gantenerumab

CL (L/day)	Q (L/day)	V_2 (L)	V_3 (L)	k_a (1/d)	F1 (1/d)	D (1/d)
0.336	0.869	3.152	6.38	0.22	0.494	0.0821

An update of the population PK model parameters was not considered as newly available drug concentrations were within prediction ranges from the established PK model. The maximum likelihood estimation of the log hazard model parameters E_{max} and EC_{50} was performed using NONMEM software. ARIA-E events were interval censored with a cutoff at 742 days. A total of 797 patients with 50 ARIA-E events were analysed.

Parameter estimates are shown in Table 3.

Table 3 ARIA-E Parameters for Gantenerumab

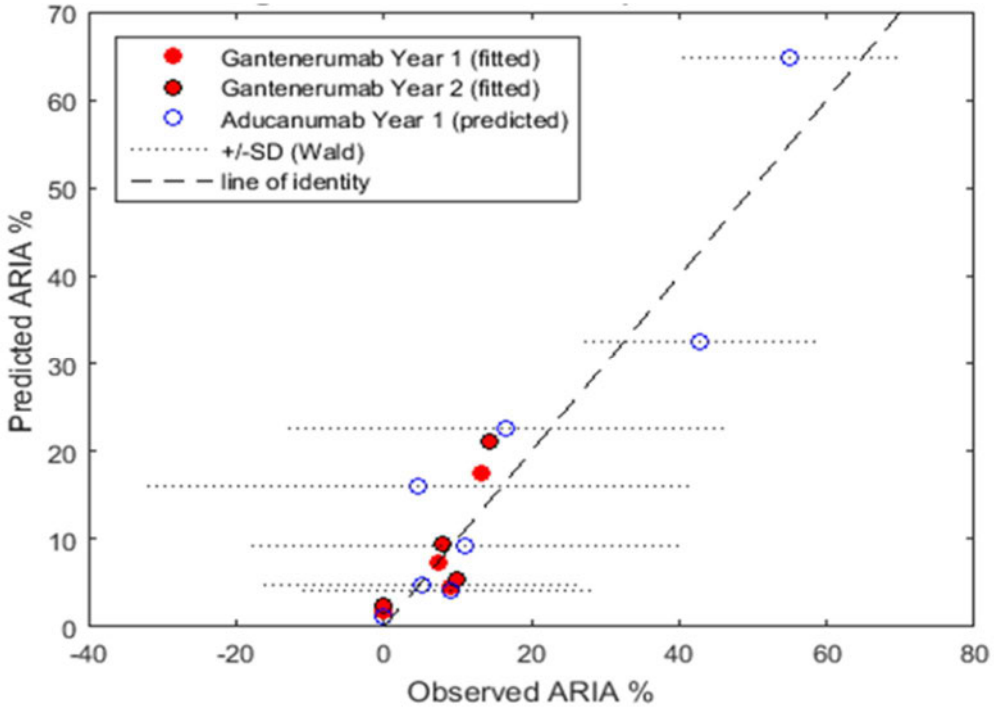
I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (μg/mL)
8.7E-6 (non-carrier) F 3.55E-5 (carrier) F	323.44 F	2.15 F	6.05±2.33	8.60±7.13

amyloid-related imaging abnormality–edema/effusion; F = fixed.

On inspection of the aducanumab PRIME study data (Sevigny et al. 2015), it became clear that the PK properties of gantenerumab and aducanumab are very similar. This supported an opportunity to test the hazard PK-PD model applied to gantenerumab on IV aducanumab ARIA-E data. The ARIA-E model, which already provides a good description of the gantenerumab ARIA-E data in Study WN25203 after 1 and 2 years of treatment, respectively, also predicted the aducanumab Phase Ib ARIA-E data with a great degree of accuracy (see Figure 1), including the ARIA rate differences across *APOE* ε4 allele groups (see Figure 2), even though this approach is limited based on external aggregated data. This finding indicated that doses much larger than those

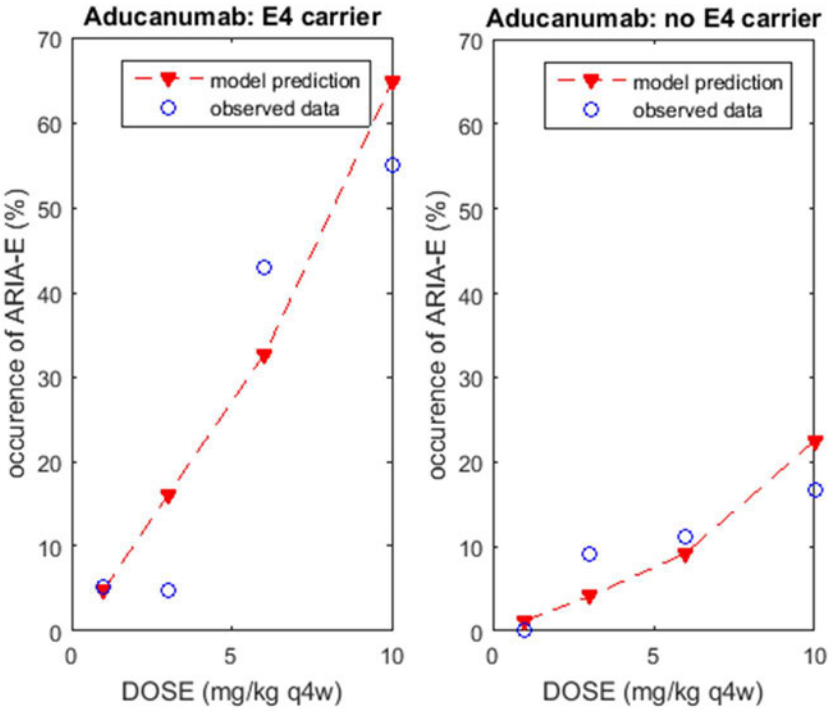
given in Study WN25203 can be described by the hazard model, provided that a constant dose regimen is used.

Figure 1 ARIA-E Prediction for IV Aducanumab Using Bapineuzumab Hazard Model Adapted to SC Gantenerumab



ARIA = amyloid-related imaging abnormality; ARIA-E = amyloid-related imaging abnormality–edema/effusion; IV = intravenous; SC = subcutaneous; SD = standard deviation.

Figure 2 Model-Based Predictions of ARIA-E Occurrence for Aducanumab by *APOE ε4* Carrier and Non-Carrier Status and Dose for a Q4W Dosing Regimen: Comparison to Observed Data in the PRIME Study



APOE ε4= apolipoprotein E, allele ε4; ARIA = amyloid-related imaging abnormality; ARIA-E = amyloid-related imaging abnormality–edema/effusion; IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous.

3. ARIA EVENTS UNDER DOSE TITRATION REGIMENS

3.1 MODELING DATABASE AS OF 6 DECEMBER 2016

To check the validity of the model under titration conditions, two patient groups were selected from the open-label extension studies of WN25203 and WN28745. The first group comprised 71 patients who received increasing doses of gantenerumab and received placebo during the double-blind phase of the study. The second group comprised 417 patients who received a constant dose of gantenerumab and who did not have treatment-free intervals of more than 70 days. The first group is representative for the intended Phase III design, and the second group was included to enhance the database and link the model to previously established results (see Table 4).

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Table 4 Patient Population Included in ARIA-E Model Building (Database as of 6 December 2016)

Number of Patients (Number of Events)	Study WN25203	Study WN28745	Total	Comment
Total included in study	**797 (63)**	**371 (35)**	**1168 (108)**	
Placebo treatment	236 (2)	111 (3)	347 (5)	Excluded from model building
Total included in study on active drug	**561 (61)**	**260 (32)**	**821 (103)**	
Total on active drug before OLE, or treatment gaps >70 days	125 (11)	108 (23)	333 (44)	Excluded from model building
Total included in model building	**436 (50)**	**52 (9)**	**488 (59)**	
Titrated without prior treatment	19 (1)	52 (9)	71 (10)	Included in model building
Constant dosing, and treatment gaps <70 days	417 (49)	—	417 (49)	Included in model building

ARIA-E = amyloid-related imaging abnormality–edema/effusion; OLE = open-label extension.

As noted previously, the maximum likelihood estimation was performed using NONMEM software. Estimated model parameters were E_{max} , EC_{50} and the baseline risk for carriers and non-carriers. ARIA-E events were observation interval censored.

Parameter estimates are shown in Table 5.

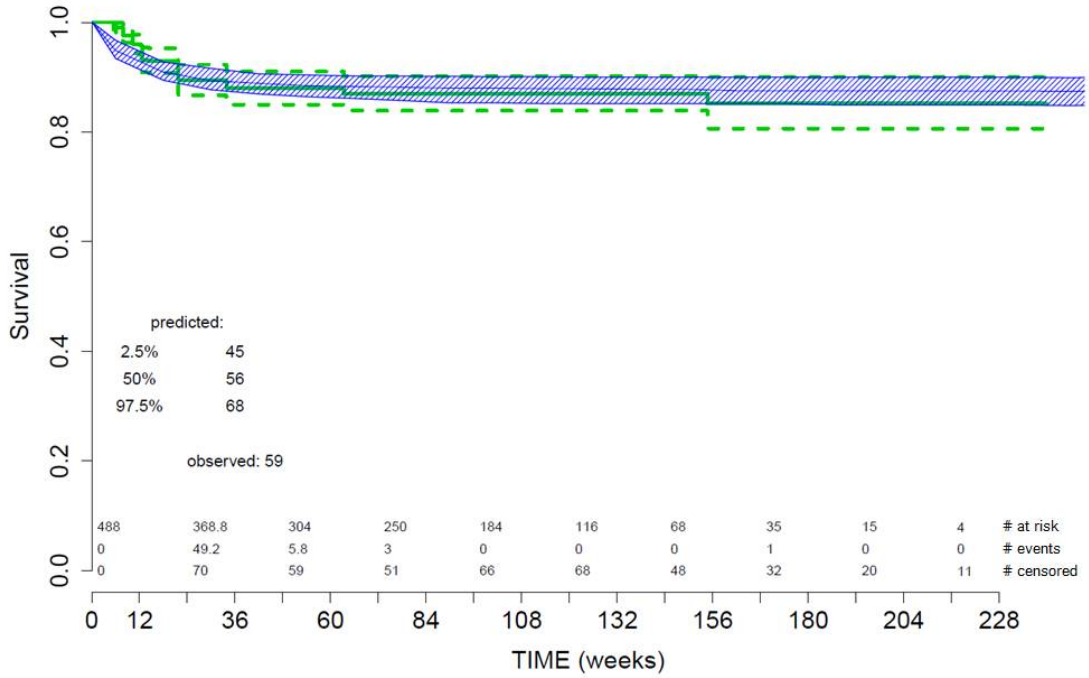
Table 5 ARIA-E Parameters for Gantenerumab When Applied to Titration Data

I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (μg/mL)
5.84 ± 4.22 E-6 (non-carrier) 11.9 ± 7.30 E-6 (carrier)	323.44 F	2.15 F	7.12 ± 1.03	5.16 ± 2.85

ARIA-E = amyloid-related imaging abnormality–edema/effusion; F = fixed.

Visual predictive checks were performed to assess model performance. As shown in Figure 3, the overall model performance was acceptable. Figure 4 presents a condition that was excluded from the model building. The apparent bias in the prediction might be attributable to a SCarlet RoAD study effect, which will be followed up during ongoing completion of the database.

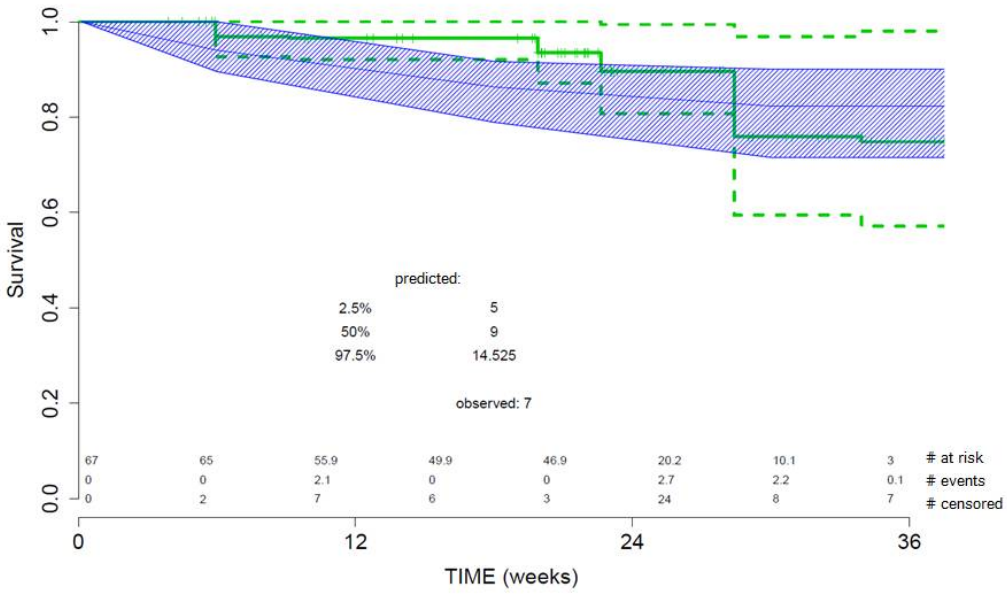
Figure 3 Visual Predictive Check on Database Used for Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% [median], and 97.5%) and the actual observed number of events.

Figure 4 Visual Predictive Checks: Patients in SCarlet RoAD Study with Treatment Interruption >70 Days from Time 0 at Start of Open-Label Extension WN25203



ARIA-E = amyloid-related imaging abnormality–edema/effusion; OLE = open-label extension.
Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% [median], and 97.5%) and the actual observed number of events.

3.2 MODELING DATABASE AS OF 3 MARCH 2017

Table 6 presents an updated ARIA-E model building using data based on the cutoff date of 3 March 2017. In Table 7, ARIA-E parameters for gantenerumab are summarized when applied to titration data.

Table 6 Patient Population Included in ARIA-E Model Building (Database as of 3 March 2017)

Number of Patients (Number of Events)	Study WN25203	Study WN28745	Total	Comment
Total included in study	**797 (69)**	**371 (60)**	**1168 (129)**	
Placebo treatment	234 (2)	108 (3)	342 (5)	Excluded from model building
Database cleaning ongoing	3 (0)	—	3 (0)	Excluded from model building
Total included in study on active drug	**560 (67)**	**263 (57)**	**823 (124)**	
Long-term constant dose before titration	64 (9)	83 (17)	147 (26)	Excluded from model building
Total included into model building	**496 (58)**	**180 (40)**	**676 (98)**	
Titrated without prior treatment	24 (2)	67 [18]	91 (20)	Included in model building
Doses always smaller or equal to 225 mg	472 (56)	113 (22)	585 (78)	Included in model building

ARIA-E = amyloid-related imaging abnormality–edema/effusion.

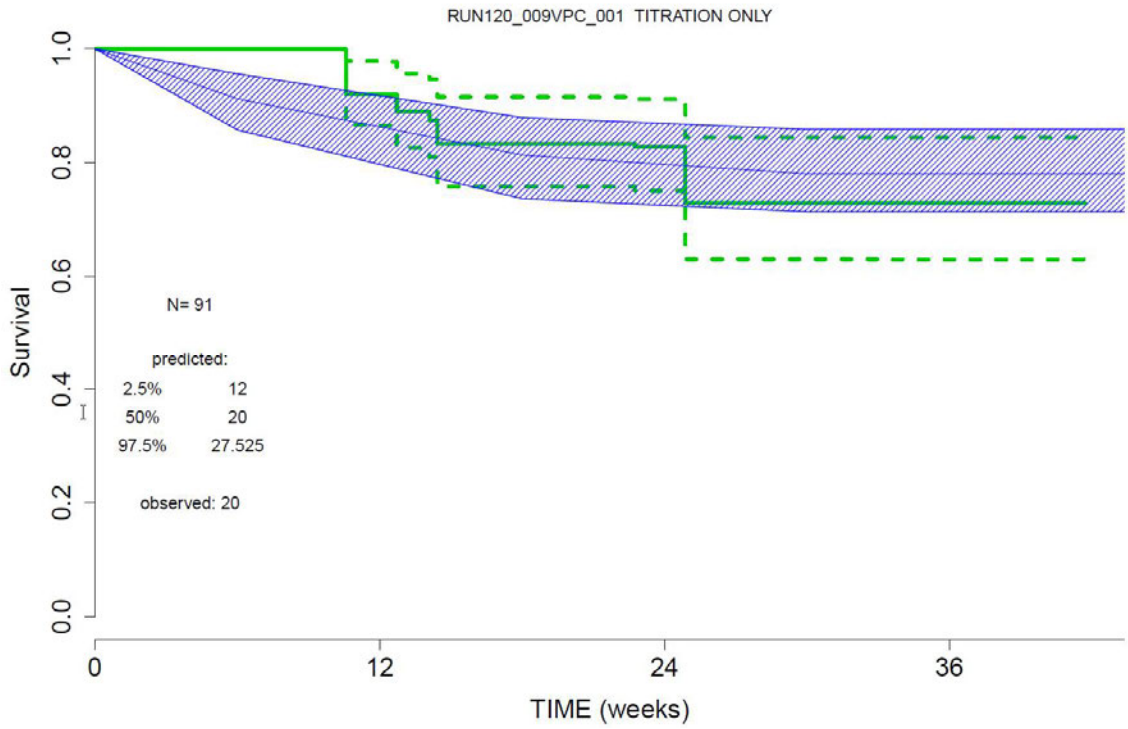
Table 7 ARIA-E Parameters for Gantenerumab when Applied to Titration Data

I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (µg/mL)
2.36 ± 1.01 E-5 (non-carrier) 3.75 ± 1.30 E-5 (carrier)	323.44 F	2.15 F	6.07 ± 0.702	7.75 ± 2.70

ARIA-E = amyloid-related imaging abnormality–edema/effusion; F = fixed.

Figures 5–7 show visual predictive checks for the final model. For both patients groups selected for model building, the diagnostics look acceptable (see Figures 5 and 6). For the excluded patient group who exhibited constant gantenerumab dosing followed by titration, often with 1 to 2 years of treatment gap in between, the diagnostics indicate a considerable mismatch. This could not be corrected by introducing covariates (such maximum treatment gap) into the model. It appears that the hazard model with its time component is not flexible enough for such regimens.

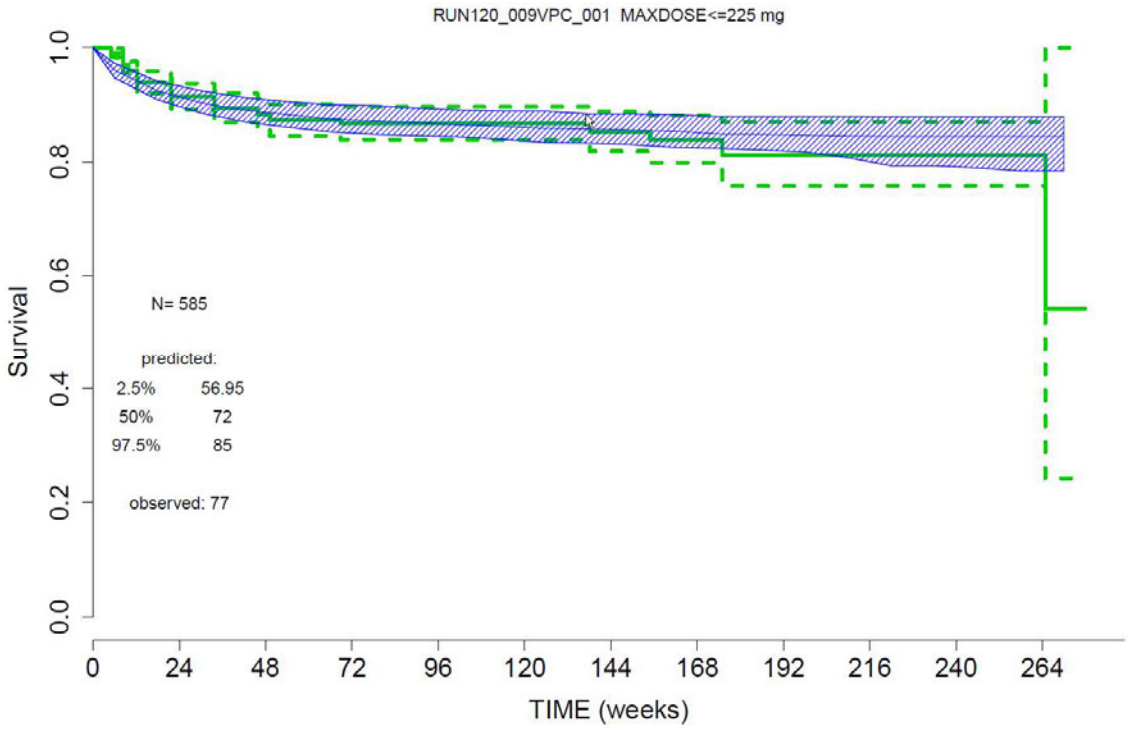
Figure 5 Visual Predictive Check on Titration Data Used for Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events (2.5%, 50% [median], and 97.5% percentiles), and the actual observed number of events. The apparent mismatch over the first 12 weeks is because no scan was performed during this period. Survival refers to the ARIA-E event-free proportion.

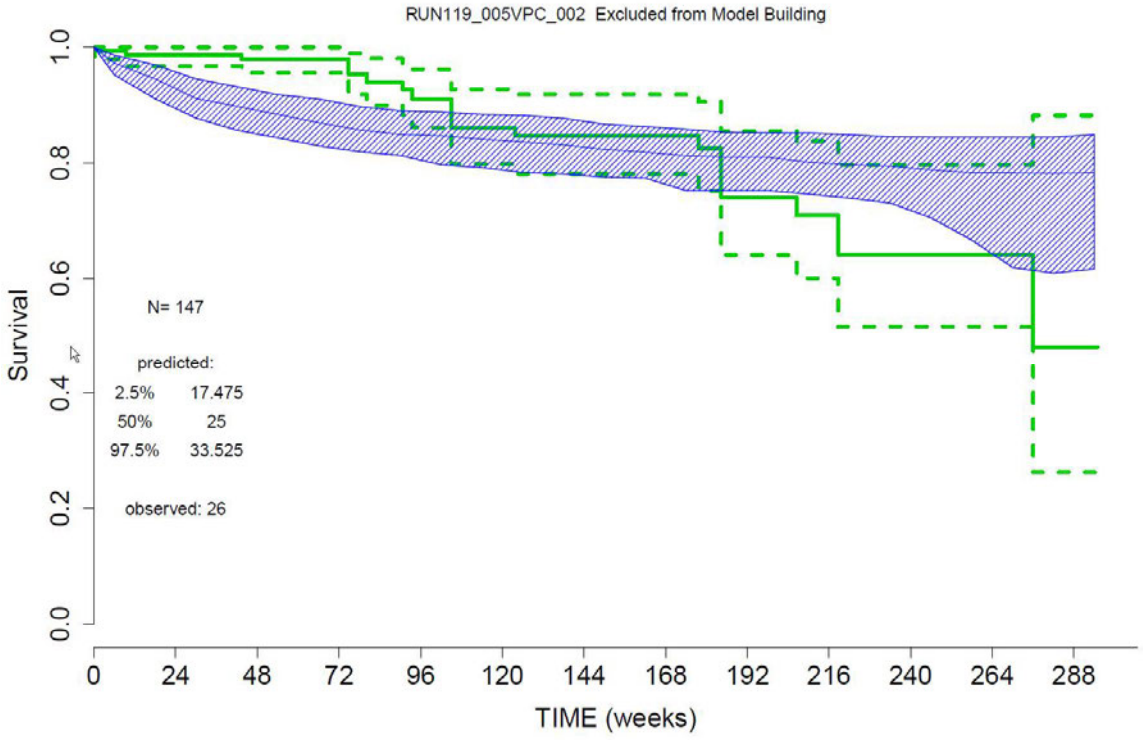
Figure 6 Visual Predictive Check on Data Used for Model Building (Based on Data from Patients Enrolled in the Double-Blind WN25203 and WN28745 Studies and Dosed with 225 mg)



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% (median), and 97.5%) and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

Figure 7 Visual Predictive Check on Excluded Data from Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% (median), and 97.5%) and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

3.3. MODELING DATABASE AS OF 8 JULY 2017

Table 8 presents an updated ARIA-E model building using data based on the cutoff date of 8 July 2017. In Table 9, ARIA-E parameters for gantenerumab are summarized when applied to titration data.

Table 8 Patient Population Included in ARIA-E Model Building (Database as of 7 July 2017)

Number of Patients (Number of Events)	Study WN25203	Study WN28745	Total	Comment
Total included in study	797 (75)	371 (60)	1168 (135)	
Placebo treatment	227 (2)	108 (3)	335 (5)	Excluded from model building
Database cleaning ongoing	2 (0)	—	2 (0)	Excluded from model building
Total included in study on active drug	568 (73)	263 (57)	831 (130)	
Long-term constant dose before titration	66 (14)	80 (16)	146 (30)	Excluded from model building
Total included into model building	502 (59)	183 (41)	685 (100)	
Titrated without prior treatment	36 (3)	70 (19)	106 (22)	Included in model building
Doses always smaller or equal to 225 mg	466 (56)	113 (22)	579 (78)	Included in model building

ARIA-E = amyloid-related imaging abnormality–edema/effusion.

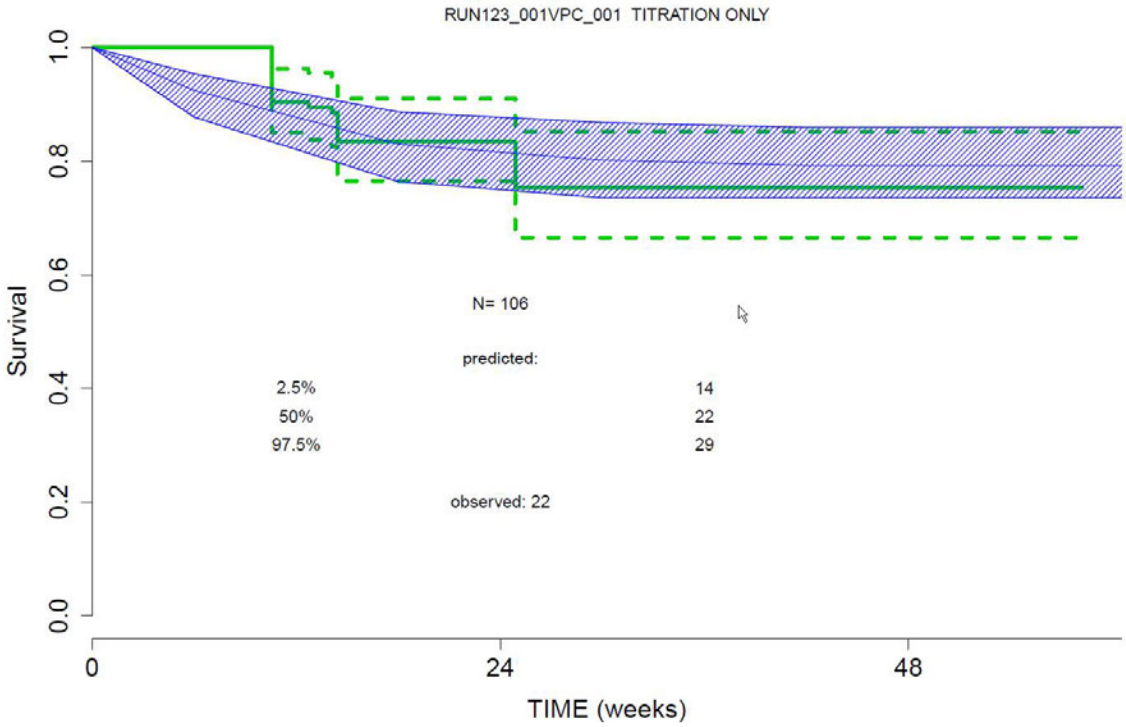
Table 9 ARIA-E Parameters for Gantenerumab when Applied to Titration Data

I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (μg/mL)
2.14 ± 0.9742 E-5 (non-carrier) 3.52 ± 1.24 E-5 (carrier)	323.44 F	2.15 F	5.92 ± 0.688	6.78 ± 2.88

ARIA-E = amyloid-related imaging abnormality–edema/effusion; F = fixed.

Figures 8–10 show visual predictive checks for the final model. For both patients groups selected for model building, the diagnostics look acceptable (see Figures 8 and 9). For the excluded patient group who exhibited constant gantenerumab dosing followed by titration, often with 1 to 2 years of treatment gap in between, the diagnostics indicate a considerable mismatch. This could not be corrected by introducing covariates (such maximum treatment gap) into the model. It appears that the hazard model with its time component is not flexible enough for such regimens.

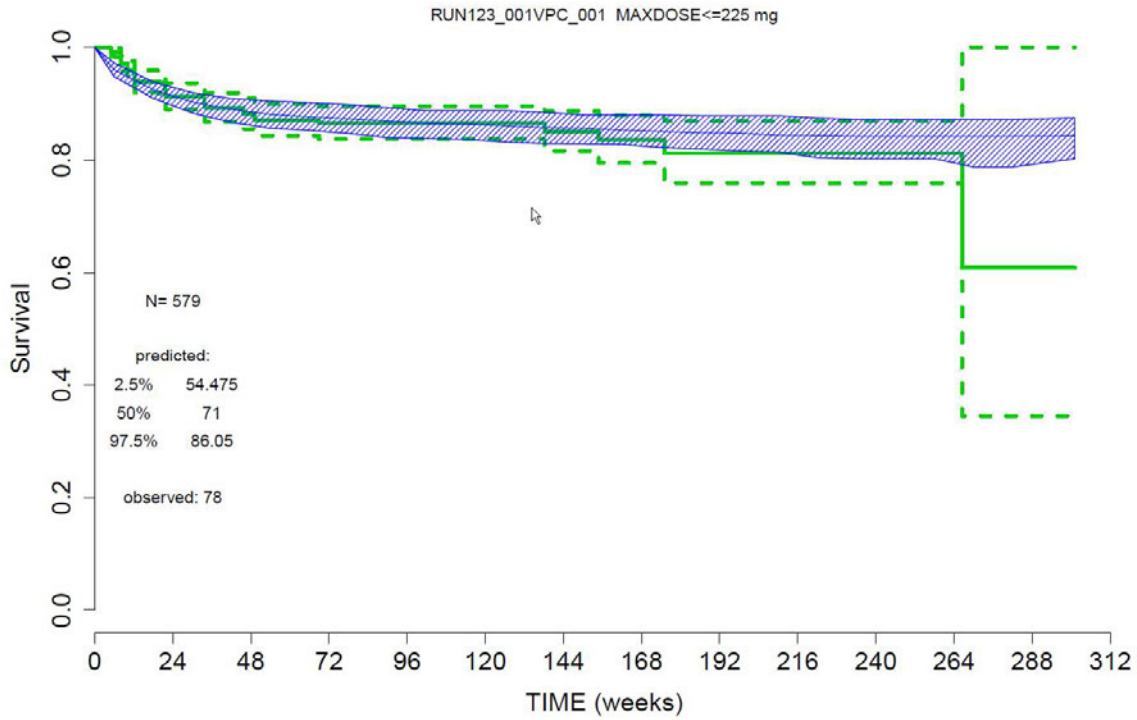
Figure 8 Visual Predictive Check on Titration Data Used for Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events (2.5%, 50% [median], and 97.5% percentiles), and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

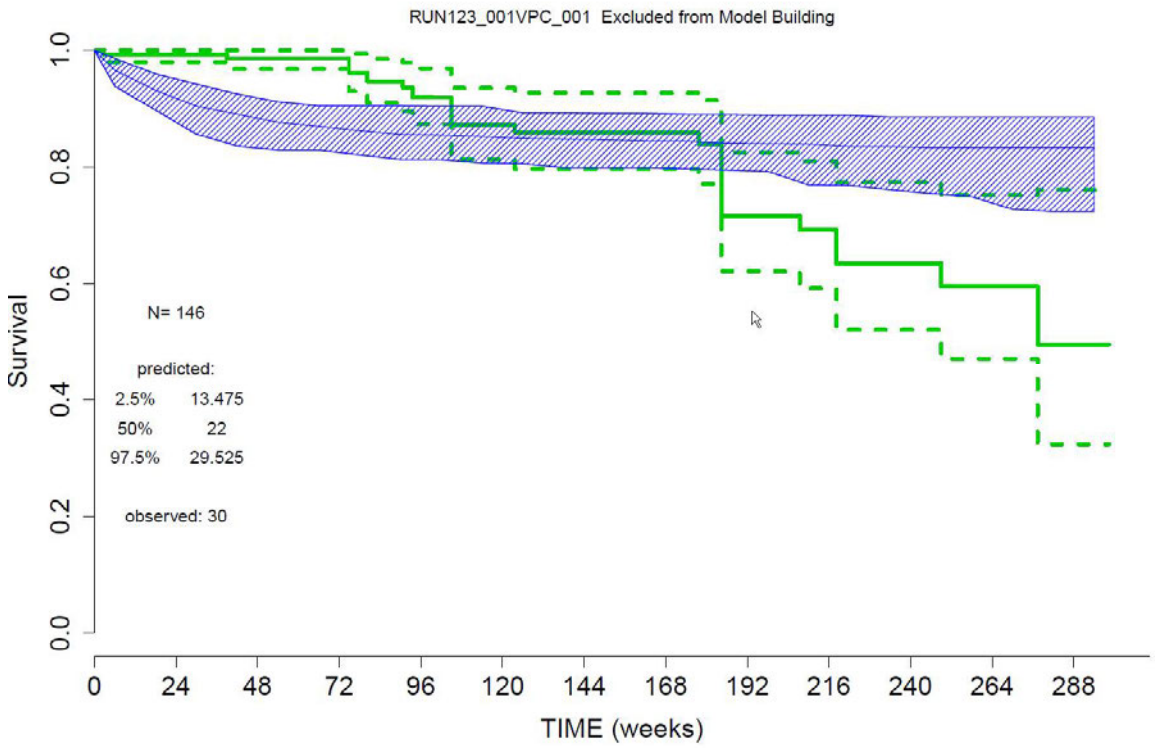
Figure 9 Visual Predictive Check on Data Used for Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% (median), and 97.5%) and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

Figure 10 Visual Predictive Check on Excluded Data from Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% (median), and 97.5%) and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

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Hutmacher M, Hu C, Guenzler-Pukall V, et al. Pharmacokinetic-pharmacodynamic modeling of amyloid-related imaging abnormalities of edema following administration of bapineuzumab to subjects with mild to moderate Alzheimer's disease [poster]. Presented at the American Conference on Pharmacometrics 2013.

Sevigny J, Chiao P, Williams L, et al. Randomized, double-blind, Phase 1b study of BIIB037 in patients with prodromal or mild Alzheimer's disease. 12th International Congress on Alzheimer's and Parkinson's Disease. Symposium 26 March 2015. Nice, France.

Appendix 6
Management Rules for Amyloid-Related Imaging Abnormalities

Event	Characteristics	Action to Be Taken
ARIA-E	Asymptomatic ARIA-E and BGTS <4	• Continue study drug at the same dose level (i.e., do not uptitrate) and repeat MRI scan 4 weeks later. – As long as BGTS is <4 and ≥1, continue study drug at the same dose level and repeat MRI 4 weeks later. – Once ARIA resolves, resume uptitration and obtain an MRI scan per the titration schedule. For participants randomized to the Q2W regimen, perform another MRI scan 3 months after $ARIA\ resolution$.
	Symptomatic ARIA-E (of any size) or asymptomatic ARIA-E and BGTS ≥4	• Temporarily interrupt study drug and perform MRI scans at 4-week intervals until symptoms and ARIA-E resolve. • When symptoms and ARIA-E resolve, reintroduce study drug at dose given at the time the event was detected. – Perform an MRI scan before next scheduled dose for participants randomized to the Q4W regimen or after the second dose for participant randomized to the Q2W regimen. – If no new ARIA-E is detected, resume uptitration and obtain an MRI per titration schedule. For participants randomized to the Q2W regimen, perform another MRI scan 3 months after study drug reintroduction.
	Any recurrence of ARIA-E	• Treat the same as the first event (based on symptoms and BGTS).
ARIA-H	>15 ARIA-H cumulatively (should not include any disseminated LH)	• Discontinue study drug.

Appendix 6: Management Rules for Amyloid-Related Imaging Abnormalities (cont.)

ARIA-E = amyloid-related imaging abnormality–edema/effusion; ARIA-H=amyloid-related imaging abnormality–hemosiderin deposition; BGTS=Barkhof grand total score; LH=leptomeningeal hemosiderosis; MRI=magnetic resonance imaging;Q2W=every 2 weeks.

In exceptional cases of (1) an ARIA-E that is asymptomatic with BGTS <4 and considered stable over consecutive MRI images by the Sponsor and investigator; or (2) symptomatic ARIA-E for which the imaging evidence of ARIA-E has resolved but the CNS symptoms continue, study drug can be either reintroduced or uptitrated, as applicable, and 4-weekly MRI monitoring may no longer be necessary, as determined by the Sponsor and investigator.

Symptomatic ARIA-E is defined as onset or worsening of CNS symptom(s) that is/are temporally associated with ARIA-E MRI findings

A PK and a plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria

GRADUATE I (PROTOCOL WN29922)

SUMMARY OF CHANGES

A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, PARALLEL-GROUP, EFFICACY, AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE

PROTOCOL AMENDMENT, VERSION 2:

RATIONALE

Protocol WN29922 has been amended to present the results of the relative bioavailability study (WP40052) and to adjust the dosing regimen of Study WN29922 according to these results. In addition, the entry criteria of the study population have been reviewed to increase the homogeneity of the study population and to better target the right population (early Alzheimer's).

The changes below, along with a rationale for each, have been updated as follows:

- Data from the World Health Organization on Alzheimer's disease has been updated (Section 1.1).
- Safety and efficacy data from open-label extension (OLE) WN25203 and WN28745 studies have been updated. Figure 4 (OLE Results 6−9 Months at High Dose) has been added; subsequent figures have been renumbered accordingly (Sections 1.2.2, 1.2.2.3, 1.2.2.4, 1.2.3, 1.3.1, 1.3.2, 1.3.5).
- Language in the clinical studies section has been updated to reflect recent information from the relative bioavailability study (WP40052) (Section 1.2.2.5).
- The dosing regimen has been adjusted to reflect the results of the relative bioavailability study WP40052 (Sections 1.3.2, 1.3.3, 1.3.5, 3.3.1, 3.3.3, 3.3.4, 4.3.1.1, and 4.3.2.1, and Table 1, Figure 6, and Appendix 1).
- The key secondary designation has been removed; consequently the hierarchization of the secondary endpoints has also been removed. Section 3.3.7 has been deleted; subsequent sections have been renumbered accordingly (Sections 2 and 6.4.2).
- The Coding (also called Digit Symbol Substitution Test) has been added to the secondary endpoints to have a broader range of cognitive domains assessed (Sections 2, 4.5.5.1, 4.5.5.6, 4.6.2, 4.6.5, 4.6.6, and Appendix 1). Section 4.5.5.6 has been added and subsequent sections have been renumbered accordingly.
- Language has been updated to reflect changes in the study design, including China extension enrollment and analyses (Sections 3.1.1, 3.2, 3.3.1, 4.1, 4.2, 6, 6.1, and 6.8).
- For operational reasons, the Mini-Mental State Examination has been added to the optional prescreening, and the screening period has been extended by 4 weeks (Sections 3.1.1, 3.2, and 4.6.1 and Appendix 1).
- Inclusion and exclusion criteria have been updated to clarify the criteria and to further improve the safety and data quality (Sections 4.1.1, 4.1.2.1, 4.1.2.3, 4.1.2.6, and 4.1.2.7).
- With respect to blinding, the roles of the study personnel have been refined to clarify and improve the blinding (Sections 4.3.2.1 and 4.5.5.1).
- Wording around the regulatory status of the amyloid positron emission tomography (PET) tracers has been added (Section 4.3.2.2) and the PET tracer safety reporting process has been clarified (Sections 5.3.1 and 5.4.2.1).

- It has been clarified that benzodiazepine used to treat a mood or anxiety disorder as maintenance treatment is not permitted medication (Section 4.4.1).
- Cognitive, functional, and health economics assessments have been clarified to include descriptive categories, recall periods, and total score ranges as appropriate (Sections 4.5.5.1, 4.5.5.8, 4.5.5.9, 4.5.5.10, and 4.5.5.13).
- A biomarker serum sample has been added at screening and subsequent visits to allow additional analyses (Section 4.5.6.2 and Appendix 1).
- Patient non-compliance rules have been adapted to be applicable to every 4-week and every 2-week dosing regimens (Section 4.7.2).
- Reporting requirements for medical device complaints have been included (Sections 5.3 and 5.4.4).
- Reporting of serious adverse events and adverse events of special interest has been modified to be until the patient's last visit (including long-term follow-up visits) (Section 5.3.1 and 5.4.2.2). As a result, Section 5.6 "Adverse Events That Occur after the Adverse Event Reporting Period" has been deleted and subsequent sections have been renumbered.
- It has been clarified that sites are not expected to review the clinical outcome assessment data for adverse events (Section 5.3.5.14).
- Language has been changed for clarity and consistency regarding reporting of injection-site reactions (Section 5.3.5.2).
- Medical monitor information has been updated to reflect a change in the Medical Monitor (Section 5.4.1).
- The determination of sample size and an increase in sample size have been clarified (Section 6.1).
- The ARIA model has been updated (Section 3.3 and Appendix 5; Table 8, Table 9, and Figures 8−10 have been added to Appendix 5).
- To summarize the list of the prohibited medications, a table has been added as Appendix 7.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 3:

RATIONALE

Protocol WN29922 has been amended to clarify the sample size of this study. While protocol wording allowed an increase of up to 1140 patients based on factors external to the study, the Sponsor wanted to clarify that upon initial learnings from external studies, a decision was made to increase the power of the study. Thus, the sample size has been increased from 760 participants per study to 1016 (508 patients randomized to gantenerumab and 508 randomized to placebo). This is described in detail in Section 6.1. In addition, Protocol WN29922 has been amended to allow the first patients enrolled in the study to enroll in an open-label extension (OLE) as planned. Details on this procedure and the OLE schedule of activities have been added.

Changes to the protocol, along with a rationale for each change, are summarized below:

- Language in the clinical studies section has been updated to reflect the most recent safety and efficacy information from the OLE WN25203 and WN28745 studies (Sections 1.2.2.3, 1.2.2.4, 1.2.3, 1.3.1)
- The objectives and endpoints section has been updated to include the objectives and endpoints for the OLE period of the study (Section 2)
- Details on the OLE procedures, such as eligibility, assessments, study duration, and follow-up have been added (Sections 3.1.1, 3.2, 3.3.4.2, 3.3.5, 4.1.1, 4.1.3, 4.2, 4.3.2.2, 4.6.4, 4.6.6, 4.6.7, 4.7.1, Appendix 1)
- Further details on the China Enrollment Plan have been provided (Sections 3.1.1, 4.1, 6.8)
- The China Food and Drug Administration (CFDA) is now called the National Medical Products Administration (NMPA), and the terms in the protocol have been updated accordingly (Sections 3.1.1, 4.1, 6)
- Additional substudy details, including details related to the optional interim analyses, have been provided (Sections 3.1.2, 6.4.3, 6.7.2)
- Sample size-related information has been updated as described above (Sections 4.1, 6, 6.1)
- Time windows for certain study visits and procedures have been clarified (Sections 4.3.2.1, 4.3.2.2, 4.5.5, 4.6.1, 4.6.3, 4.6.4, 5.1.2, Appendix 1)
- Language has been added to clarify that GV-971 is not a permitted medication in this study (Sections 4.1.1, 4.1.2.7, 4.4.1)
- Language has been added to clarify that body weight should be obtained each time creatinine clearance is tested and that genitourinary system examination is optional (Section 4.5.3, Appendix 1)
- Language has been added to clarify that a plasma sample should be collected along with the pharmacokinetic sample each time the site becomes aware of the occurrence or worsening of ARIA-E or the occurrence of ARIA-H meeting discontinuation criteria (Sections 4.5.6.2, 5.1.2, Appendix 1)
- Wording in the immunogenicity section has been clarified (Section 5.1.1.3)
- Management of patients who experience select adverse events has been clarified (Sections 5.1.2, 5.3.5.1, Appendix 6)
- Language related to injection reactions (Section 5.3.5.2) and abortions (Section 5.4.3.2) has been updated

- Emergency medical contact information has been updated (Section 5.4.1)
- The procedures for reporting adverse events that occur after the adverse event reporting period (Section 5.6) and for expedited adverse event reporting have been clarified (Section 5.7)
- Exploratory efficacy analyses have been added (Section 6.4.3)
- Appendix 7 has been removed

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 4:
RATIONALE

Protocol WN29922 has been amended in response to the COVID-19 pandemic due to the SARS-CoV-2 virus. Restrictions imposed globally during the COVID-19 pandemic are expected to affect protocol-specified activities, including administration of study drug, and could decrease the power of the study. This amendment extends the double-blind treatment period by 12 weeks in order to mitigate the impact of missed administrations and to preserve the scientific integrity of the study by enabling more participants to receive study drug at the initially intended exposures. The continuing impact of the COVID-19 pandemic on study procedures will be closely monitored, and if there are greater than anticipated disruptions to study drug administration, the amendment also allows the option o further extending the double-blind treatment period by another 12 weeks. These extension periods are described in Section 3.3.4.1. For the same reason, the upper limit of the sample size has been increased from 1140 to 1322 (Section 6.1).

Please note that the extension of treatment by 12 or 24 weeks is not expected to adversely impact the risks/benefits that were previously described for this study.

Changes to the protocol, along with a rationale for each change, are summarized below:

- Data from the World Health Organization on Alzheimer's disease has been updated (Section 1.1).
- In the Objectives and Endpoints section (Section 2), wording has been changed from “Week 104” to “Week 116” to accommodate the study extension of 12 weeks or to “Week 128” to accommodate the study extension of 24 weeks (12 weeks plus an additional 12 weeks if applicable) (Table 2).
- The description of the study was clarified to include a description of 2 scenarios due to COVID-19 related disruptions. In scenario 1, participants who are active in the double-blind treatment period after implementation of Protocol Version 4 will have the double-blind treatment period extended by 12 weeks, up to Week 116. In scenario 2, participants who are active in the double-blind treatment period after implementation of Protocol Version 4 will have the double-blind treatment period extended by an additional 12 weeks, up to Week 128 (Section 3.1.1). Participants who have completed the double-blind treatment period prior to implementation of Protocol Version 4 will continue into the OLE or safety follow-up periods following Week 104 assessments, as per the original schedule.
- The descriptions of the length of the double-blind treatment period and the total study length were updated to reflect the study extension(s) of 12 weeks or 24 weeks (12 weeks plus an additional 12 weeks if applicable) of the double-blind treatment period (Section 3.2).
- Appendix 1 was updated to incorporate the double-blind treatment period extension(s).
- For CSF-enrolled patients, the optional CSF collection timepoint was shifted from Week 52 to Week 76 (Appendix 1) in order for CSF to be collected between screening and the final efficacy and safety visit of the double-blind treatment part of the study.
- The number and/or timing of dosing visits, assessments, study completion visits, and follow-up assessments was updated to reflect the two possible double-blind treatment period extensions (Sections 4.3.2.1, 4.6.3, 4.6.6, 4.6.7).
- Use of approved monoclonal antibodies (except to prevent or postpone cognitive

decline) has been removed from the Exclusion Criteria (Section 4.1.2) and Prohibited Medications (Section 4.4.2) because their use has become more common within the study population. These drugs do not raise any safety concerns if used in the study and are not expected to have drug-drug interactions with gantenerumab.

- The timing of the primary efficacy outcome measure was updated to accommodate the study extension(s) of 12 weeks or 24 weeks (12 weeks plus an additional 12 weeks if applicable) (Section 6.4.1).
- The timing of the planned interim analysis was changed from 24 months to 116 weeks (or to 128 weeks, if the study is extended by an additional 12 weeks) after 50% of the targeted study enrollment has been reached (Section 6.7.1).
- The protocol now states that every effort will be made to minimize missing data and to expedite the implementation of Protocol Version 4 (Section 6.4.1).
  In case a participant's study partner changes, collection of data using the Zarit Caregiver Interview□Alzheimer's Disease (ZCI) scale will continue (rather than stop) in order to minimize missing data (Section 4.5.5.9).
- The volume of the blood sample collected for plasma biomarker assessment was increased by 6 mL to ensure that the volume is sufficient for analyses (Section 4.5.6.2).
- Wording was added to indicate that unused PK sample material may also be used for the assessment of exploratory plasma biomarkers in order to align with the ICF (Section 4.5.6.4).
- "Patient" has been replaced with "participant" as appropriate throughout to be consistent with current best practices for studies of Alzheimer's disease.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

The changes to the protocol, along with a rationale for each change, are summarized below:

- Section 1.3.5 Overall Benefit-Risk Summary has been updated to address the COVID-19 pandemic impact on the Benefit-Risk assessment for Study WN29922 as per the MHRA requirement
- Objectives and endpoints of the Double-Blind Treatment Period (Table 2) have been updated in the following manner:

  – Corresponding endpoints for the 'exploratory efficacy' objective have been revised to remove 'in global outcome' as a criteria for the measurement of change from baseline to Week 116, which was added in error.

  – The exploratory endpoint 'Time to clinically evident decline, defined as an increase of ≥2.0 in CDR-SOB subscore or ≥1 in at least four items of the FAQ' has been removed from Table 2, as it is not considered relevant anymore based on new available data.
  – The exploratory endpoint 'Change from baseline to Week 116 measured by 'Function as assessed by the CDR function subscore" has been removed as it is no longer considered relevant based on new available data.
  – The exploratory endpoint 'clinically evident decline as measured using the CDR' has been added to Table 2.
  – The pharmacokinetic (PK) objective of the study has been changed to an exploratory PK objective to be consistent with the sparse PK sampling design and population modeling used to analyse the dose concentration–time data of gantenerumab. In addition, the protocol has been amended to enable early access PK, anti-drug antibodies (ADA) and pharmacodynamic (PD) biomarker samples. Early access will only be applied if there are sufficient sample data available to make an adequate assessment.
  – The corresponding endpoints for the pharmacodynamic (PD) biomarker objective have been revised to clarify the duration of change as a measurement from baseline to Week 116 when assessing brain amyloid load, brain tau load and cerebral spinal fluid markers.
  – The PD biomarker objective endpoint 'MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all participants ' has been reclassified as exploratory as it is no longer considered secondary based on new available data.
- Sections 3.1.1 and 4.1.3 have been updated to clarify that the open-label extension (OLE) of Study WN29922 is not applicable in countries that cannot run Study WN42171.
- Sections 4.1.2.7, 4.4.1, 4.7.2, and Appendix 1 have been revised to clarify the Medical Monitor's responsibility to review and support patient cohort management and other protocol activities. Any reference to approval by the Medical Monitor with regards to medical decisions following enrollment has been removed from the protocol. The Principal Investigator (PI) may consult with the Medical Monitor/Sponsor for advice or clarification and may share risk factor information pertinent to the patient, but the medical decisions for the study participants are the responsibility of the PI.
- Section 4.1.3 has been amended to replace Week 104 with Week 116 (or Week 128, if applicable) which was omitted in the previous protocol amendment.

- Sections 4.6.3 and 4.6.4 have been amended to better clarify the order of assessments during the study visits
- Section 6.4.1 has been updated according to the estimand framework outlined in the ICH-E9 draft addendum with regards to the primary endpoint.
- Section 6.4.2 has been updated to remove the reference to time to event, which was included in error.
- Sections 6.4.4, 6.5 and 6.6 have been updated to clarify that a separate cut off may be necessary for PD biomarker, PK, and ADA samples to allow early access to PD biomarker samples and ensure expedient data analyses.
- Section 6.7.1 and 6.7.2 have been updated to include additional details surrounding the conduct of an interim analysis, should one be implemented.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY, AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH *EARLY (*PRODROMAL TO MILD*)* ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN39658
VERSION NUMBER:	2
EUDRACT NUMBER:	2017-001365-24
IND NUMBER:	102,266
TEST PRODUCT:	Gantenerumab (RO4909832)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 21 July 2017
DATE AMENDED:	Version 2: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

PROTOCOL AMENDMENT, VERSION 2: RATIONALE

Protocol WN39658 has been amended to present the results of the relative bioavailability study (WP40052) and to adjust the dosing regimen of Study WN39658 according to these results. In addition, the entry criteria of the study population have been reviewed to increase the homogeneity of the study population and to better target the right population (early Alzheimer's).

The changes below, along with a rationale for each, have been updated as follows:

- Data from the World Health Organization on Alzheimer's disease has been updated (Section 1.1).
- Safety and efficacy data from open-label extension (OLE) WN25203 and WN28745 studies have been updated. Figure 4 (OLE Results 6–9 Months at High Dose) has been added; subsequent figures have been renumbered accordingly (Sections 1.2.2, 1.2.2.3, 1.2.2.4, 1.2.3, 1.3.1, 1.3.2, 1.3.5).
- Language in the clinical studies section has been updated to reflect recent information from the relative bioavailability study (WP40052) (Section 1.2.2.5).
- The dosing regimen has been adjusted to reflect the results of the relative bioavailability study WP40052 (Sections 1.3.2, 1.3.3, 1.3.5, 3.3.1, 3.3.3, 3.3.4, 4.3.1.1, and 4.3.2.1, and Table 1, Figure 6, and Appendix 1).
- The key secondary designation has been removed; consequently the hierarchization of the secondary endpoints has also been removed. Section 3.3.7 has been deleted; subsequent sections have been renumbered accordingly (Sections 2 and 6.4.2).
- The Coding (also called Digit Symbol Substitution Test) has been added to the secondary endpoints to have a broader range of cognitive domains assessed (Sections 2, 4.5.5.1, 4.5.5.6, 4.6.2, 4.6.5, 4.6.6, and Appendix 1). Section 4.5.5.6 has been added and subsequent sections have been renumbered accordingly.
- Language has been updated to reflect changes in the study design, including China extension enrollment and analyses (Sections 3.1.1, 3.2, 3.3.1, 4.1, 4.2, 6, 6.1, and 6.8).
- For operational reasons, the Mini-Mental State Examination has been added to the optional prescreening, and the screening period has been extended by 4 weeks (Sections 3.1.1, 3.2, and 4.6.1 and Appendix 1).
- Inclusion and exclusion criteria have been updated to clarify the criteria and to further improve the safety and data quality (Sections 4.1.1, 4.1.2.1, 4.1.2.3, 4.1.2.6, and 4.1.2.7).
- With respect to blinding, the roles of the study personnel have been refined to clarify and improve the blinding (Sections 4.3.2.1 and 4.5.5.1).

- Wording around the regulatory status of the amyloid positron emission tomography (PET) tracers has been added (Section 4.3.2.2) and the PET tracer safety reporting process has been clarified (Sections 5.3.1 and 5.4.2.1).
- It has been clarified that benzodiazepine used to treat a mood or anxiety disorder as maintenance treatment is not permitted medication (Section 4.4.1).
- Cognitive, functional, and health economics assessments have been clarified to include descriptive categories, recall periods, and total score ranges as appropriate (Sections 4.5.5.1, 4.5.5.8, 4.5.5.9, 4.5.5.10, and 4.5.5.13).
- A biomarker serum sample has been added at screening and subsequent visits to allow additional analyses (Section 4.5.6.2 and Appendix 1).
- Patient non-compliance rules have been adapted to be applicable to every 4-week and every 2-week dosing regimens (Section 4.7.2).
- Reporting requirements for medical device complaints have been included (Sections 5.3 and 5.4.4).
- Reporting of serious adverse events and adverse events of special interest has been modified to be until the patient's last visit (including long-term follow-up visits) (Section 5.3.1 and 5.4.2.2). As a result, Section 5.6 "Adverse Events That Occur after the Adverse Event Reporting Period" has been deleted and subsequent sections have been renumbered.
- It has been clarified that sites are not expected to review the clinical outcome assessment data for adverse events (Section 5.3.5.14).
- Language has been changed for clarity and consistency regarding reporting of injection-site reactions (Section 5.3.5.2).
- Medical monitor information has been updated to reflect a change in the Medical Monitor (Section 5.4.1).
- The determination of sample size and an increase in sample size have been clarified (Section 6.1).
- The ARIA model has been updated (Section 3.3 and Appendix 5; Table 8, Table 9, and Figures 8–10 have been added to Appendix 5).
- To summarize the list of the prohibited medications, a table has been added as Appendix 7.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY, AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH *EARLY* (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN39658
VERSION NUMBER:	2
EUDRACT NUMBER:	2017-001365-24
IND NUMBER:	102,266
TEST PRODUCT:	Gantenerumab (RO4909832)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return the signed original of this form to the Sponsor or its designee. Please retain a signed copy of the form for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY, AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH *EARLY* (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**
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IND NUMBER:	102,266
TEST PRODUCT:	Gantenerumab (RO4909832)
PHASE:	Phase III
INDICATION:	Alzheimer's disease
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy and safety of gantenerumab compared with placebo in patients with *early* (prodromal to mild) *Alzheimer's disease* (AD). Specific objectives and corresponding endpoints for the study are outlined below.

Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of gantenerumab administered by SC injection compared with placebo	• The change from baseline (Day 1) to Week 104 in global outcome, as measured by the CDR-SOB
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo on cognition and function	The change from baseline to Week 104 in cognition and/or function, as measured by: • MMSE total score • ADAS-*Cog11 and* ADAS-Cog13 • Verbal Fluency Task • *Coding* • FAQ • ADCS-ADL total score *and instrumental score*
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo	The change from baseline to Week 104 in the following: • Time to clinically evident decline, defined as an increase of ≥2.0 in CDR-SOB subscore or ≥1 in at least four items of the FAQ • *Severity*, as assessed by the CDR Global Score • Function, as assessed by the CDR function subscore • Dependence level, as derived from the ADCS-ADL score • Cognition, as measured by the CDR cognition subscore • Health-related quality of life, as assessed by the QoL-AD scale • Behavioral and *neuropsychiatric* symptoms of AD, as measured by the NPI-Q • Study partner burden, as assessed by the ZCI-AD scale • Elements of resource utilization, as assessed by the RUD-Lite • Health outcomes in patient and study partner, as measured by EQ-5D questionnaire

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

Objectives and Corresponding Endpoints (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of gantenerumab compared with placebo	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Presence of ADAs during the study relative to the presence of ADAs at baseline
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the PK profile of gantenerumab	• Plasma concentration of gantenerumab (administered subcutaneously) at specified timepoints
Pharmacodynamic Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo in patients with *early* (prodromal to mild) Alzheimer's disease	• Change from baseline in brain amyloid load, as measured by amyloid PET scan in a subset of patients • Change from baseline in brain tau load, as measured by tau PET scan in a subset of patients • Change from baseline in cerebral spinal fluid markers of disease in a subset of patients, including, but not limited to, $A\beta_{1-42}$, total tau, and phosphorylated tau • MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all patients
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo in patients with *early* (prodromal to mild) Alzheimer's disease	Plasma pharmacodynamic biomarkers Change from baseline to Week 104 in functional brain connectivity, as measured by resting-state functional MRI (where available) Change from baseline to Week 104 in *integrity of white matter*, as measured by DTI-MRI (where available)

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

Study Design

Description of Study

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of gantenerumab in patients with *early (*prodromal to mild*)* AD.

The planned number of patients for the global enrollment phase for the study is approximately *760* patients: randomized in a 1:1 ratio to receive gantenerumab and placebo (*380* patients randomized to gantenerumab and *380* randomized to placebo). To maintain a balanced number of patients enrolled in each treatment arm and to ensure that the arms are comparable, randomization will be stratified by stage of disease (prodromal AD vs. mild AD), apolipoprotein E (*APOE)* allele status (presence vs. absence of the ε4 allele), use of AD medication (presence vs. absent), geographic region *(Western Europe vs. Rest of the World vs. North America)* and participation in longitudinal amyloid *and tau* positron emission tomography (PET) *substudies*. Approximately *175* centers in approximately *15* countries worldwide will participate in this study.

Patients will be selected on the basis of clinical diagnosis of probable AD (according to the National Institute on Aging/Alzheimer's Association [NIA/AA] diagnostic criteria and guidelines for AD) or prodromal AD (according to the NIA/AA diagnostic criteria and guidelines for mild cognitive impairment (MCI) due to AD). *The aim of the study is to recruit approximately 50% of the participants with prodromal AD.*

Eligible patients will be 50–90 years old, inclusive, must show evidence of β-amyloid pathology as indicated by the cerebral spinal fluid (CSF) tau to $A\beta_{42}$ ratio (CSF-enrolled patients) or positive amyloid PET scan by visual read (PET-enrolled patients), and meet eligibility criteria.

The study will consist of a screening period of up to *12* weeks in length following the signing of informed consent. *Sites also have* the option to prescreen patients on the Free and Cued Selective Reminding Test (FCSRT) *and Mini-Mental State Examination (MMSE).* Patients must sign a separate Informed Consent Form before administration of *these tests* if used for prescreening. If the results confirm a patient's eligibility, then the FCSRT *and MMSE* will not have to be completed again during the screening period as long as the test has been done within 12 weeks prior the baseline.

Eligible patients will then undergo baseline visit assessments (Day 1) prior to receiving the first dose of blinded study drug (gantenerumab or placebo). Patients will continue in the double-blind treatment period for 104 weeks. Visits and study drug administration will occur every 4 weeks (Q4W) until patients reach the *target dose*, which will be *510* mg every 2 weeks (Q2W). After the last dose of study drug (Week 102), final efficacy and safety assessments will be performed 2 weeks later (Week 104). Patients may then enroll in a*n* open-label extension (OLE) study *if eligible*. Patients who do not enter the OLE study will have additional follow-up visits at 14 and 50 weeks after the last dose for safety and limited efficacy assessments (Weeks 116 and 152, respectively). *Patients who prematurely discontinue treatment will continue in the double-blind treatment period and will be asked to return for collection of safety and limited efficacy data.*

Patients will undergo brain magnetic resonance imaging (MRI) examinations for safety monitoring and longitudinal changes in brain structure. MRI scans will be read by a central MRI reader. Patients will also undergo standard tests to monitor safety (blood tests, ECG), as well as the Columbia–Suicide Severity Rating Scale (C-SSRS) to monitor for suicidality, tests for cognition, function, and quality-of-life (QoL) status. Blood samples for the assessment of pharmacokinetic (PK) samples, pharmacodynamic (PD) biomarkers, and anti-drug antibodies will be obtained from all patients.

The incidence and nature of adverse events, serious adverse events, amyloid-related imaging abnormalities–edema/effusion (ARIA-E) and ARIA–hemosiderin deposition (ARIA-H), adverse events of special interest, ECGs, and laboratory abnormalities will be assessed on a regular basis by an unblinded independent Data Monitoring Committee (iDMC).

The study consists of three distinct periods:

- Screening *(including an optional prescreening)*: The screening period may last up to *12* weeks for each eligible patient.
- Double-blind treatment period: After screening, patients who meet all eligibility criteria will be randomly assigned to one of two arms (gantenerumab or placebo) in a 1:1 ratio. Following baseline assessments, each patient will receive a minimum of nine SC Q4W administrations of study drug (uptitration period), followed by up to 34 SC Q2W administrations of study drug in the 104-week, double-blind treatment period. The last dose of study drug will be administered at Week 102. At the end of the double-blind treatment period, all participants will undergo a Week 104 visit in order to collect data for the primary analyses.
- Post–double-blind treatment period: After the Week 104 visit, patients will be asked to come back for the long-term follow-up visits or to continue in the OLE.

  Long-term follow-up: Long-term follow-up will consist of a 50-week follow-up period with evaluations at Weeks 14 and 50 after completion of study drug administration or early termination for patients who do not enter the OLE.

  OLE study: All eligible patients will have the opportunity to enter an OLE study (details will be provided in a separate protocol).

China Enrollment Plan

Based on historical data, patient recruitment are expected to take longer in China; therefore, a specific China enrollment plan has been established. Thus, if at least 1 patient is enrolled *at sites* in *mainland* China*, Hong Kong, and Taiwan that are recognized by the China Food and Drug Administration (CFDA)* during the global enrollment phase, additional patients may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. All patients enrolled *at CFDA-recognized sites* in the global enrollment *phase* will be included in the primary analysis.

Substudies

The substudies associated with Study WN39658 will be described in separate protocols, and patients consenting to enroll in these substudies will be asked to sign the associated Informed Consent Forms.

Data Monitoring Committee

The iDMC will evaluate patient safety and efficacy on a regular basis. In addition to the data defined in the iDMC Charter (e.g., the incidence and nature of adverse events, serious adverse events, and adverse events of special interest, ARIA-E and ARIA-H), the iDMC will review all necessary cumulative data at regular intervals during the study, including efficacy when needed. It is anticipated that these assessments will occur approximately every 3 months. At the time of each review, the iDMC will make appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, the treatment regimen should be modified, the protocol should be amended, enrollment should be held pending further safety evaluations). The iDMC will also evaluate planned *or unplanned* interim analyses for efficacy or futility.

Decisions will be made in consideration of the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities will be detailed in the iDMC Charter.

Final decisions will rest with the Sponsor.

Number of Patients

The planned enrollment specifies approximately *760* patients.

Target Population

This study will enroll approximately *760* patients with increased brain amyloid burden (defined according to CSF or PET criteria), objective memory impairment indicated by cognitive assessment, and a diagnosis of probable AD or prodromal AD based on relevant NIA/AA criteria during the global enrollment phase.

An increase in sample size may be considered in the event of changes to the sample size assumptions on the basis of blinded data review or factors external to the study.

If at least 1 patient is enrolled *at sites* in *mainland* China*, Hong Kong, and Taiwan that are recognized by the CFDA* during the global enrollment phase, additional patients may be enrolled in a China extension to ensure a *total enrollment that is* sufficient *to support* registration in China. All patients enrolled *at CFDA-recognized sites* in the global enrollment phase will be included in the primary analysis.

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Ability to provide written consent signed by the patient (co-signed by the patient's legally authorized representative, if required by the local regulations, guidelines, and independent Ethics Committee or Institutional Review Board)
- Age 50–90 years old at screening, inclusive
- Availability of a person (referred to as the "study partner" throughout this protocol) who:
  - *Agrees to participate throughout the 2 years duration of study*
  - *In the investigator's judgment,* has frequent and sufficient contact (e.g., 5 times per week or approximately 10 hours per week) with the patient
  - *In the investigator's judgment, is* able to provide accurate information regarding the patient's cognitive and functional abilities, *including knowledge about domestic activities, hobbies, routines, social skills, and basic activities of daily life; work and educational history; cognitive performance including memory abilities, language abilities, temporal and spatial orientation, judgment and problem solving; emotional and psychological state; and can report any changes in the general health status*
  - Agrees to provide information *and to complete all aspects of the study* at clinic visits (which require partner input for scale completion)
  - Signs the necessary Informed Consent Form(s), and has sufficient cognitive capacity to accurately report on the patient's behavior *as well as* cognitive and functional abilities
  - Is *fluent* in *the language used at the site and has* sufficiently good general health to have a high likelihood of maintaining the same level of interaction with the patient and participation in study procedures throughout the duration of the study

    Every effort should be made to have same study partner participate throughout the duration of the study.
- Fluency in the language of the tests used at the study site
- Willingness and ability to complete all aspects of the study (including MRI, lumbar puncture [if applicable], clinical genotyping, and PET imaging [if applicable])

  The patient should be capable of completing assessments either alone or with the help of the study partner.
- Adequate visual and auditory acuity, in the investigator's judgment, sufficient to perform the neuropsychological testing (eye glasses and hearing aids are permitted)
- Evidence of AD pathological process, as confirmed by CSF tau/$A\beta_{42}$ or on amyloid PET scan by qualitative read by the core/central PET laboratory
- Demonstrated abnormal memory function at screening (FCSRT cueing index ≤ 0.67 and free recall ≤ 27)
- Screening MMSE score ≥ 22 and CDR-GS of 0.5 or 1.0

- Probable AD dementia (consistent with NIA/AA core clinical criteria for probable AD dementia) or prodromal AD (consistent with the NIA/AA diagnostic criteria and guidelines for mild cognitive decline due to AD)
- If the patient is receiving symptomatic AD medications, a stable dosing regimen for at least 3 months prior to baseline and until randomization
- Agreement not to donate blood or blood products for transfusion for the duration of the study and for 1 year after final dose of study drug
- Agreement not to participate in other research studies for the duration of this trial and its associated substudies
- For enrollment in the China extension, *patients must have residence in mainland China, Hong Kong, or Taiwan and be of Chinese ancestry.*
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least *16* weeks after the last dose of study drug

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

Exclusions Related to Central Nervous System Disorders

Patients who meet any of the following criteria related to central nervous system (CNS) disorders will be excluded from study entry:

- Any evidence of a condition other than AD that may affect cognition, including, but not limited to, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, *Parkinson* disease, corticobasal *syndrome*, Creutzfeldt-Jakob disease, progressive supranuclear palsy, frontotemporal *lobar* degeneration, Huntington disease, normal pressure hydrocephalus, seizure disorder, delirium or hypoxia
- History or presence of clinically evident *systemic* vascular disease (e.g., clinically significant carotid/vertebral *artery* stenosis or plaque, aortic aneurysm*),* that in the opinion of the investigator has the potential to affect cognitive function
- *History or presence of clinically evident cerebrovascular disease (e.g., intracranial or cerebral vascular malformations, aneurysm, intracranial macrohemorrhage)*

  Patients with asymptomatic developmental venous anomalies may be eligible after discussion with and approval by the Medical Monitor.
- *History or presence of posterior reversible encephalopathy syndrome*
- History or presence of any stroke with clinical symptoms within the past 12 months, or documented history within the last 6 months of an acute event that is consistent, in the opinion of the investigator, with a transient ischemic attack
- History of severe, clinically significant (persistent neurologic deficit or structural brain damage) CNS trauma (e.g., cerebral contusion)
- History or presence of intracranial mass (e.g., glioma, meningioma) that could potentially impair cognition

- Presence of infections that affect brain function or history of infections that resulted in neurologic sequelae (e.g., HIV, syphilis, neuroborreliosis, and viral or bacterial meningitis and encephalitis)
- History or presence of systemic autoimmune disorders that potentially cause progressive neurologic disease with associated cognitive deficits (e.g., multiple sclerosis, lupus erythematosus, anti–phospholipid antibody syndrome, and Behçet disease)
- History of schizophrenia, schizoaffective disorder, major depression, or bipolar disorder

  History of major depression is acceptable if patient has had no episode within the past year or is considered in remission or depression is controlled by treatment.
- At risk for suicide in the opinion of the investigator
- Alcohol and/or substance abuse or dependence (according to the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, Version 5) within the past 2 years

  Nicotine use is allowed.

  Marijuana use is not allowed and must be discontinued at least 3 months before screening.

Imaging-Related Criteria

Patients who meet any of the following imaging criteria will be excluded from study entry:

- According to the MRI central reader, MRI evidence of any of the following:
  - $>$ 2 lacunar infarcts
  - Any territorial infarct $>$ 1 cm^3
  - Any white matter lesion that corresponds to an overall Fazekas score of 3 that requires at least one confluent hyperintense lesion on the fluid-attenuated inversion recovery (FLAIR) sequence, which is $\geq$ 20 mm in any dimension
- Combined number of microbleeds and areas of leptomeningeal hemosiderosis (i.e., cumulative ARIA-H) on MRI more than five (and should not include any disseminated leptomeningeal hemosiderosis) based on the review performed by the central reader prior to randomization
- Presence of any other significant cerebral abnormalities, including ARIA-E, as assessed on MRI
- Inability to tolerate MRI procedures or contraindication to MRI, including, but not limited to, presence of pacemakers not compatible with MRI, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan, or any other clinical history or examination finding that, in the judgment of the investigator, would pose a potential hazard in combination with MRI

Cardiovascular Disorders

Patients who meet any of the following criteria related to cardiovascular disorders will be excluded from study entry:

- History or presence of clinically symptomatic atrial fibrillation requiring maintenance therapy

  Patients who experienced non-valvular atrial fibrillation that resolved more than 1 year ago and was not associated with prior stroke are eligible.
- Within the last year, unstable or clinically significant cardiovascular disease (e.g., myocardial infarction)

  Heart failure classified as New York Heart Association Class I or II cardiac disease is allowed if not associated with hospitalization within the previous 12 months.
- Uncontrolled hypertension (e.g., blood pressure generally $>$160 mmHg systolic or $>$95 mmHg diastolic)

Hepatic and Renal Disorders

Patients who meet any of the following criteria related to hepatic and renal disorders will be excluded from study entry:

- Chronic kidney disease, indicated by creatinine clearance <30 mL/min to be calculated by the central laboratory using the Cockcroft-Gault formula at screening, which remains <30 mL/min if retested
- Confirmed and unexplained impaired hepatic function as indicated by screening AST or ALT $\geq 3\times$ the upper limit of normal (ULN) or total bilirubin $\geq 2\times$ ULN

Infections and Immune Disorders

Patients who meet any of the following criteria related to infections and immune disorders will be excluded from study entry:

- History of, or known to currently have HIV infection, or hepatitis B or hepatitis C infection that has not been adequately treated in the opinion of the investigator, or history of spirochete infection of the CNS (e.g., syphilis, Lyme disease, or borreliosis)
- Systemically, clinically significantly immunocompromised patients, owing to continuing effects of immune-suppressing medication

Metabolic and Endocrine Disorders

Patients who meet any of the following criteria related to metabolic and endocrine disorders will be excluded from study entry:

- Abnormal thyroid function as indicated by abnormal screening tests that are judged to be clinically significant by the investigator, or abnormal thyroid function that requires a new treatment or an adjustment of current treatment

  A patient may be rescreened if there is no improvement in cognition in the investigator's judgment after 3 months of adequate treatment for thyroid function.
- *Patients with evidence of folic acid deficiency (as indicated by folic acid level below the lower limit of normal) or vitamin B-12 deficiency (as indicated by vitamin B-12 level below the lower limit of normal and/or methylmalonic acid levels above ULN)*

  A patient may be rescreened if there is no improvement in cognition after 3 months of adequate treatment for folic acid or vitamin B-12 deficiency.
- Screening hemoglobin A_{1c} (HbA_{1C}) >8% (retesting is permitted if slightly elevated) or poorly controlled insulin-dependent diabetes (including hypoglycemic episodes)

  A patient may be rescreened after 3 months to allow optimization of diabetic control.

Exclusions Related to Medications

The following medications are prohibited for a pre-specified duration prior to study start, as indicated, and during the entire period of study participation (Patients who start these medications during the study may be withdrawn from study treatment):

- Any previous administration of gantenerumab or active immunotherapy (vaccine) that is being evaluated to prevent or postpone cognitive decline
- Any passive immunotherapy (immunoglobulin) or other long–acting biologic agent that is under evaluation to prevent or postpone cognitive decline within 1 year of screening
- Any other investigational treatment or any other treatment with a monoclonal antibody within 5 half-lives or 4 months prior to screening, whichever is longer
- Any previous treatment with medications specifically intended to treat Parkinson symptoms or any other neurodegenerative disorder within 1 year of screening and with no *plans to initiate such medications* prior to randomization

  Certain medications are acceptable if the patient is taking the medicine for a non-neurodegenerative disorder, such as restless leg disorder (e.g., pramipexole).

- Typical antipsychotic or neuroleptic medication within 6 months of screening and with no planned changes prior to randomization except as brief treatment for a non-psychiatric indication (e.g., emesis)

  Atypical antipsychotic medications are not allowed except for intermittent short-term use and will need to be discontinued 2 days or *at least* 5 half-lives (whichever is longer) prior to any neurocognitive assessment.
- Anti-coagulation medications within 3 months of screening with no *plans to initiate any* prior *to* randomization

  Anti-platelet treatments (e.g., aspirin, clopidogrel, and dipyridamol) are permitted.

  Short-term, perioperative use of anticoagulant medications will not result in permanent discontinuation from the study; however, any such use must be discussed prospectively with the Medical Monitor and may require temporary study drug interruption.
- Chronic use of opiates or opioids (including long-acting opioid medication) within 3 months of screening with no *plans to initiate any* prior *to* randomization

  Intermittent short-term use of short–acting opioid medications for pain is permitted except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.
- Stimulant medications (amphetamine, methylphenidate preparations, or modafinil) within 1 month of screening and throughout the study
- Chronic use of benzodiazepines, barbiturates, or hypnotics from 3 months before screening and with no *plans to initiate any* prior *to* randomization

  Intermittent short-term use of benzodiazepines, buspirone, or short-acting hypnotic medication for sleep or anxiety is allowed except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

Other Exclusions

Patients who meet any of the following criteria will be excluded from study entry:

- Other causes of intellectual disability that may account for cognitive deficits observed at screening (e.g., static encephalopathy, closed brain injury, mental retardation)

  This may be based on, for example, patient's sufficient education or work experience.
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study
- Deformity of the lumbosacral region of the spine that in the opinion of the investigator would contraindicate lumbar puncture in patients who will have lumbar puncture
- Clinically significant abnormal screening blood, CSF (if applicable), or urine results that remain abnormal at retest
- Impaired coagulation (screening prothrombin time [PT] $> 1.2 \times$ the ULN that remains abnormal on retest)
- History of cancer, with the following exceptions:
  - If considered to be cured
  - If not being actively treated with anti-cancer therapy or radiotherapy and, in the opinion of the investigator, is not likely to require treatment in the ensuing 5 years
  - For prostate cancer or basal cell carcinoma, no significant progression over the previous 2 years
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins, including gantenerumab
- Hypersensitivity to any of gantenerumab excipients
- Any other severe or unstable medical condition that, in the opinion of the investigator or Sponsor, could be expected to progress, recur, or change to such an extent that it could put the patient at special risk, bias the assessment of the clinical or mental status of the patient to a significant degree, interfere with the patient's ability to complete the study assessments, or would require the equivalent of institutional or hospital care

- Residence in a skilled nursing facility such as a convalescent home or long-term care facility: Patients who subsequently require residence in such facilities during the study may continue in the study and be followed for efficacy and safety, provided that they have a study partner who meets the minimum requirement

End of Study

The end of the study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for safety analyses or safety follow-up is received for the last patient, whichever occurs later.

Length of Study

The study will consist of a screening period of up to 12 weeks (including the optional prescreening period) for each eligible patient who signs the Informed Consent Form and agrees to participate, followed by a double-blind treatment period of 102 weeks of study drug treatment plus a visit 2 weeks after the last dose (Week 104), and followed by the post–double-blind treatment period of two follow-up visits at 14 and 50 weeks after the last dose (Weeks 116 and 152, respectively). Thus, for a patient not entering the OLE, the maximum length of study is approximately 164 weeks.

Investigational Medicinal Products

The investigational medicinal product for this study is gantenerumab.

Test Product (Investigational Drug)

Gantenerumab or placebo will be administered by SC injection to all patients.

Gantenerumab will be administered by SC injection to all patients randomized to the active treatment arm, regardless of *APOE* ε4 status, at a dose of 120 mg SC Q4W for 3 months, 255 mg SC Q4W for 3 months, and 510 mg SC Q4W for 3 months, prior to reaching the target dose. Once the target dose is reached, study drug will be administered every 2 weeks (Q2W administration of 510 mg SC gantenerumab). The switch to a Q2W administration schedule allows decreasing the number of SC administrations in the abdomen per visit.

For Q4W injections, a time window of ±7 days is allowed for dosing visits. Once study drug is administered Q2W, the time window for dosing visits is ±3 days.

Regardless of dose, each patient will undergo up to a total of 43 dosing visits in the study. Injections will be administered as one 0.8-mL (120-mg dose), one 1.7-mL (255-mg dose), or two 1.7-mL injections (510-mg dose) subcutaneously to the abdomen, respectively.

Placebo of identical composition (except protein) and identical volume to gantenerumab will be administered by SC injection to all patients randomized to placebo at the same frequency and using the same route of administration.

On study drug administration days that include efficacy assessments, study drug must be administered at the clinical site. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

At applicable sites, study drug may be administered by a trained nursing professional at the patient's home or another suitable location, if the patient has given written informed consent to participate in home nursing visits.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

PET Tracers

All patients who are enrolled in PET substudies will be assessed by PET imaging using an appropriate PET ligand. For screening, the possible amyloid PET ligands will be florbetapir, florbetaben, and flutemetamol. *According to E.U. guidance, the PET tracers used in the context of this study have been designated as non-IMP. In some regions, according to local regulations, these PET tracers may be considered to be IMP.*

In countries where the PET radioligands are approved for marketing, the approved local product information will be provided, and in countries where they are not approved for marketing, the Investigator's Brochures will be provided.

Details about the PET substudies are described in separate protocols.

Statistical Methods

Primary Analysis

The primary efficacy outcome measure is the change in CDR-SOB from baseline (Day 1) to Week 104. For the primary outcome measure, the difference in mean change from baseline to Week 104 between gantenerumab-treated patients and placebo-treated patients will be estimated. The analysis will use the ITT population, with patients grouped according to the treatment assigned at randomization. A mixed model repeated measures (MMRMs) analysis adjusting for baseline CDR-SOB score, disease stage, *APOE* ε4 status, geographic region and use of AD medication at baseline will be used to estimate the mean change from baseline to Week 104 for the primary endpoint.

The model will include the change from baseline in CDR-SOB as the dependent variable. The effects in the model will include baseline CDR-SOB score, disease stage, *APOE* ε4 status, geographic region, use of AD medication at baseline, treatment group, visit, and treatment-by-visit interaction. Visit week will be treated as the repeated variable within a patient. Disease stage, *APOE* ε4 status, geographic region, background medication at baseline, patient, treatment, and visit week will be treated as class variables. An unstructured variance-covariance structure will be applied to model the within-patient errors; in case of non-convergence, compound symmetry will be used.

The difference in the change from baseline of the patients randomized to gantenerumab from patients randomized to placebo will be estimated at each timepoint. The 95% CI and p-value for treatment difference will be presented.

All efforts will be made to minimize missing data. The Sponsor plans to request patients who discontinue early from study treatment to return for collection of safety and limited efficacy data (i.e., the primary and secondary efficacy endpoints) until Week 104. To explore the robustness of MMRM results for the primary efficacy conclusions sensitivity analyses (e.g., using multiple imputation and pattern mixture models) will be performed. Descriptive summaries of the number of patients with missing data, the timing, and reasons for discontinuation from the study will also be provided by treatment group.

Determination of Sample Size

Determination of sample size is based on patients enrolled in the global enrollment phase. In this study, approximately *760* patients will be enrolled and randomized in 1:1 ratio to each treatment arm (gantenerumab or placebo) during the global enrollment phase. A sample size increase may be considered if factors external to the study or blinded study data analysis would warrant a change to the sample size assumption.

Additional patients may be randomized during the China extension if at least 1 patient is enrolled *at sites in mainland China, Hong Kong, and Taiwan that are recognized by the CFDA* during the global enrollment phase.

The estimated sample size required to demonstrate efficacy with regard to CDR-SOB is based on the following assumptions:

- The mean change in the CDR-SOB from baseline to Week 104 is *2.5* points in the placebo arm
- A common standard deviation across treatment arms for change of approximately *2.97* from baseline to Week 104 in the CDR-SOB
- Gantenerumab has a true effect of a 30% relative reduction in deterioration of CDR-SOB

Based on these assumptions*, and using a student's T-test with equal variance,* a sample size was calculated for 80% power to detect a true treatment effect of 30% relative reduction in deterioration of CDR-SOB at a two-sided α of 0.05.

Uncertainties on parameters affecting the power (e.g., dropout rate, study drug discontinuation rate, standard deviation, and placebo decline) were assumed to be equivalent to a drop-in sample size of up to around 35% and were corrected for accordingly. This calculation leads to a total of 760 patients in the study.

The sample size may be increased from *760* up to *1140* patients (*570* patients per arm). *The* decision whether to increase sample size will be based on a blinded assessment of pooled CDR-SOB change from baseline. Further details will be described in the Statistical Analysis Plan (SAP). The assessment will be performed by the Sponsor at a specified timepoint. *The sponsor will remain blinded.* The sample size will not be reduced on the basis of this assessment. Other factors external to the study may also trigger a decision to increase sample size.

Interim Analyses

Planned Interim Analysis

An interim analysis for efficacy and futility is to be conducted approximately 24 months after 50% of the targeted study enrollment has been reached.

An independent data coordinating center will be responsible for the interim analyses and study results will only be reviewed by the iDMC. The Sponsor will remain blinded.

The iDMC may recommend stop for futility if the failure criterion is met. The failure criterion will represent a low probability of a positive study outcome given the data observed at the time of interim analysis. The failure criterion will be prespecified in the iDMC SAP.

In contrast, the iDMC may "declare the study positive for overwhelming efficacy" if the study meets the success criterion on the primary endpoint. The success criterion is defined as the p-value threshold determined by standard Lan and DeMets methodology for group sequential design using the O'Brien-Fleming boundary function. If the study continues beyond the interim analysis, the critical value at the final analysis will be adjusted accordingly.

Optional Interim Analysis

Based on availability of information pertaining to gantenerumab or other compounds with similar mode of action that may emerge during the course of this study, the Sponsor may choose to conduct an additional interim analysis for futility and/or efficacy beyond the interim analysis mentioned above.

An independent data coordinating center will be responsible for the interim analyses and study results will only be reviewed by the iDMC. The Sponsor will remain blinded.

Details of the interim analyses, including the decision to conduct the optional interim analysis, the rationale, timing, and statistical details for the analyses (such as the data that would be reviewed by the iDMC and futility or efficacy thresholds) will be documented in the Statistical Analysis Plan, and the Statistical Analysis Plan will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Aβ	amyloid-beta
AD	Alzheimer's disease
ADA	anti-drug antibody
ADAS-Cog11	Alzheimer's Disease Assessment Scale–Cognition, Subscale 11
ADAS-Cog13	Alzheimer's Disease Assessment Scale–Cognition, Subscale 13
ADCS-ADL	Alzheimer's Disease Cooperative Study Group–Activities of Daily Living
ADL	activities of daily living
APOE ε4	apolipoprotein E, allele ε4
ARIA	amyloid-related imaging abnormality
ARIA-E	amyloid-related imaging abnormality–edema/effusion
ARIA-H	amyloid-related imaging abnormality–hemosiderin deposition
AUC	area under the concentration–time curve
AUC_{inf}	*area under the concentration–time curve from Time 0 to infinity*
BOLD	blood oxygenation level-dependent
BGTS	Barkhof grand total score
CDR	Clinical Dementia Rating
CDR-GS	CDR global score
CDR-SOB	Clinical Dementia Rating–Sum of Boxes
CFDA	*China Food and Drug Administration*
C_{max}	maximum concentration
COA	clinical outcome assessment
CRO	contract research organization
CSF	cerebral spinal fluid
C-SSRS	Columbia–Suicide Severity Rating Scale
CT	computed tomography
DTI	diffusion tensor imaging
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
EQ-5D	EuroQol-Five Dimensions questionnaire
FA	fractional anisotropy

Abbreviation	Definition
FAQ	Functional Activities Questionnaire
FCSRT	Free and Cued Selective Reminding Test
FCSRT-IR	Free and Cued Selective Reminding Test–Immediate Recall
FDA	(U.S.) Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
GRE	gradient recalled echo
HbA_{1C}	hemoglobin A_{1c}
HIPAA	Health Insurance Portability and Accountability Act
HN	home nursing
ICH	International Council on Harmonisation
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ISR	injection-site reaction
ITT	intent to treat
IWG	International Working Group
IV	intravenous
IxRS	interactive voice or Web-based response system
LPLV	last patient, last visit
MAD	multiple-ascending dose
MCI	mild cognitive impairment
MMRM	mixed model repeated measure
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NIA/AA	National Institute on Aging/Alzheimer’s Association
NPI-Q	Neuropsychiatric Inventory–Questionnaire
OLE	open-label extension
PD	pharmacodynamic
PET	positron emission tomography
PK	pharmacokinetic
PT	prothrombin time
p-tau	phosphorylated tau
QoL	quality of life
QoL-AD	Quality of Life–Alzheimer's Disease

Abbreviation	Definition
Q2W	every 2 weeks
Q4W	every 4 weeks
RBR	Research Biosample Repository
rs-fMRI	resting-state functional magnetic resonance imaging
RUD-Lite	Resource Utilization in Dementia–Lite
SAD	single-ascending dose
SAP	Statistical Analysis Plan
SC	subcutaneous
SOB	Sum of Boxes
SUVr	standardized uptake value ratio
t-tau	total tau
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing
ZCI-AD	Zarit Caregiver Interview–Alzheimer's Disease

1. BACKGROUND

1.1 BACKGROUND ON ALZHEIMER'S DISEASE

The World Health Organization estimates that *around 50* million people worldwide are diagnosed with dementia and that there are *10* million new cases every year. The total number of people with dementia is estimated to reach *82* million in 2030 and will *more than* triple by 2050 to *152* million. Alzheimer's disease (AD) is the most common form of dementia, accounting for 60%–70% of cases (World Health Organization 2017). The prevalence of AD increases with age, with a global prevalence of 5%–8% in people 60 years and older. Because of its increasing prevalence, long duration, and high cost of care, AD is expected to continue to represent a major public health problem for decades to come.

There is great inter-individual variability in AD progression with survival dependent on many factors, including age at onset. In general, the clinical picture evolves from "predementia" or "prodromal AD" to mild, moderate, and then severe AD. At the early stage of AD, a slight impairment of memory, language, and visuospatial function can be observed. As AD advances, patients become progressively impaired and the burden on caregivers significantly increases. The median survival time following a diagnosis of AD strongly depends on the patient's age at diagnosis and ranges from 8.3 years for persons diagnosed with AD at 65 years old to 3.4 years for those 90 years old (Brookmeyer et al. 2002). On average, individuals live 3–9 years after diagnosis (Helzner et al. 2008) and some survive as long as 20 years.

It is well recognized that in comparison to other therapeutic domains, there is a real unmet medical need in AD therapy (Gauthier et al. 2016). To date, only five medications have received marketing approval to treat the symptoms of AD, including acetylcholinesterase inhibitors (AChEi) and N-methyl-d-aspartate receptor antagonists. These approved drugs are recognized to temporarily improve some clinical symptoms of AD in some patients but do not modify progression of the disease (Cummings et al. 2016). Recent efforts have mostly focused on therapies targeting amyloid (Bachurin et al. 2017) as these offer the most compelling therapeutic targets (Graham et al., 2017). These therapies are based on the amyloid hypothesis that posits amyloid-β (Aβ) accumulation as the primary factor driving Aβ pathogenesis (Selkoe 1991; Hardy and Selkoe 2002; Selkoe and Hardy 2016). This Aβ accumulation in the brain begins well before the development of clinical dementia in AD and causes a series of downstream events leading to synaptic dysfunction, inflammation, neurodegeneration, and clinical symptoms. For these reasons, treatments that prevent, slow, or decrease the accumulation of brain Aβ are being tested as therapeutic agents in AD.

Preclinical evidence has suggested that monoclonal Aβ antibodies may be able to remove and reduce deposition of Aβ aggregates from the brain. In transgenic animal models of AD, vaccination with Aβ or passive immunization with anti–Aβ antibodies resulted in decreased amyloidosis and in improvement of memory function in some

transgenic models cognitive function (Janus et al. 2000). Accumulating clinical evidence also supports that monoclonal Aβ antibodies can bind Aβ and promote its clearance (Salloway et al. 2009; Ostrowitzki et al. 2012), reduce deposition of Aβ aggregates, and reduce markers of neurodegeneration in the cerebral spinal fluid (CSF) (Roche Research Report No. 1066251). In a Phase I study, reduction of deposited amyloid as shown on brain amyloid positron emission tomography (PET) imaging was associated with a time and dose-related slowing of cognitive decline (Sevigny et al. 2016). Because the neurological changes associated with AD develop decades before clinical symptoms emerge, it is thought that earlier intervention may be more effective in arresting or delaying disease progression (Sevigny et al. 2016). Consequently, therapies targeting this process have the potential to significantly alter the progression of the disease. Gantenerumab, a fully human monoclonal antibody targeting aggregated forms of Aβ-like Aβ oligomers, fibrils, and plaques, is expected to address this need (Bohrmann et al. 2012).

1.2 BACKGROUND ON GANTENERUMAB

Gantenerumab (or RO4909832) is a fully human anti–Aβ peptide antibody developed by in vitro selection utilizing aggregated Aβ and in vitro maturation within a complete human Igγ, subclass-1 framework (IgG1). Gantenerumab recognizes a conformational epitope of Aβ present in aggregated Aβ and that is demonstrated for both major species of Aβ that is, $A\beta_{1-40}$ and $A\beta_{1-42}$. Gantenerumab has a molecular mass of 146.3 kDa. In vitro, gantenerumab recognizes synthetic aggregated Aβ fibrils and Aβ oligomers with high nanomolar affinity (K_D, ~0.6–1.2 nM). Based on additional in vitro studies and studies in animal models, the pharmacologic profile suggests that in humans gantenerumab may prevent, inhibit, and reduce accumulation of Aβ, which is believed to play an important role in the pathogenesis of AD.

Gantenerumab is manufactured by cell culture of a recombinant Chinese hamster ovary–K1 mammalian cell line and subsequent purification of the antibody. The gantenerumab drug substance manufacturing was optimized during development, leading to several manufacturing processes (G1, G2, and G3). Recently, the gantenerumab manufacturing process was further optimized from G3 to G4 to improve process robustness and increase overall process yield. *Drug material manufactured by G4 process will be used in Phase III clinical trials (e.g., Study WN39658).* Gantenerumab is in clinical development for patients with *early (*prodromal to mild*)* AD and is also being investigated in carriers of familial AD mutations (DIAN-TU) (Bateman et al. 2017).

Refer to the gantenerumab Investigator's Brochure for details on nonclinical and clinical studies.

1.2.1 Nonclinical Studies

1.2.1.1 Nonclinical Pharmacology

The binding characteristics of gantenerumab were engineered to achieve specific and highly sensitive recognition of the assembly structure of aggregated human $A\beta_{1-42}$ and $A\beta_{1-40}$ peptides, which are major components in Aβ plaques. Specificity was demonstrated ex vivo for genuine human Aβ plaques in AD brain slices. The minimum effective concentration for staining of human Aβ plaques is 10 ng/mL (0.07 nM).

Gantenerumab showed a concentration-dependent increase in cellular phagocytosis of human Aβ plaques by human primary cells like microglia and differentiated macrophages in a brain-slice phagocytosis assay. The measured minimal effective concentration of 10 ng/mL (0.07 nM) is consistent with the observed efficacy for human Aβ plaque binding.

In single-dose and multiple-dose studies, effective brain penetration and binding to Aβ plaques in vivo were demonstrated in various models of AD-related amyloidosis, such as the PS2APP transgenic mouse model. Gantenerumab showed significant and accumulative binding to Aβ plaques. The data indicate that there is no requirement for continuous high peripheral levels to achieve a sustained binding of gantenerumab to amyloid plaques.

The plaque binding of gantenerumab from several manufacturing processes has been evaluated. The degree of plaque binding for gantenerumab manufactured by the G1 and G2 processes was investigated by semi-quantitative fluorescence imaging and was comparable in a 2-week IV safety study in PS2APP transgenic mice at doses of 0, 2, 10, and 40 mg/kg every 3 days.

An additional study, which compared the plaque binding of gantenerumab from the G3 and G4 manufacturing processes following single IV administration to PS2APP transgenic mice at a dose level of 40 mg/kg and assessed by semi-quantitative fluorescence imaging after 7 days, indicated slightly increased target engagement of the G4 material consistent with observed differences in exposure (see Section 1.2.1.2).

Chronic treatment with gantenerumab showed significant efficacy by halting progression of amyloidosis in transgenic PS2APP, APP_{London}, and tau PS2APP mouse models of AD. Amyloid reduction was evident by prevention of new plaque formation and removal of preexisting amyloid plaques by engaging microglia cells.

1.2.1.2 Nonclinical Pharmacokinetics and Metabolism

The pharmacokinetics of gantenerumab were studied in mice, rats, and cynomolgus monkeys following IV administration. Gantenerumab pharmacokinetics were characterized by a rapid initial decrease in plasma levels during the first 24 hours, followed by a long half-life, ranging from 4 to 13 days in all species. Overall, the studies demonstrate that gantenerumab has pharmacokinetic (PK) properties similar to other IgGs.

The pharmacokinetics of gantenerumab were also studied following SC administration in cynomolgus monkeys and mice. In cynomolgus monkeys, maximum plasma levels were reached after 3 days. The average bioavailability was estimated at 76%.

Gantenerumab was shown to penetrate the brain in both the monkey and mouse. Brain penetration in the monkey was evident from analysis of CSF samples. The CSF to plasma ratios ranged from 0.006% to 0.018%. Penetration and binding to $A\beta_{1-42}$ plaques in the mouse brain were evident from immunostaining for gantenerumab of brain sections obtained from PS2APP mice dosed with gantenerumab.

Rat PK studies have been conducted to compare the pharmacokinetics of gantenerumab derived from different manufacturing processes (G1, G2, G3, and G4).

Following IV administration to rats, the pharmacokinetics of the G1 and G2 materials were similar. The area under the concentration–time curve (AUC) of the G2 material was slightly lower and accounted for about 80% of the of the G1 material. Although standard bioequivalence criteria for AUC were not met, the observed difference in AUC was not considered to have an impact on the use of the G2 material in further clinical development as the difference in AUC is small. The average terminal half-life of both materials was comparable (8.0 and 8.8 days for the G1 and G2 materials, respectively).

A study comparing the pharmacokinetics of gantenerumab derived from the G3 and G4 manufacturing processes showed that the AUC of G3 material (used in the ongoing Phase III open-label extension [OLE] studies WN25203 and WN28745) was lower compared with the G4 material that will be used in Study WN39658 (mean±SD: 932±196 and 1270±187 (μg• hr/mL)/(mg/kg), respectively. The average terminal half-life of both materials was similar (11.5 and 12.3 days for G3 and G4 materials, respectively).

1.2.1.3 Toxicology and Safety Pharmacology

Potential adverse effects in relation to the presence and destruction of $A\beta_{1-42}$ plaques were assessed in PS2APP transgenic mice that were treated with up to 375 mg/kg/wk of IV gantenerumab for up to 26 weeks. No evidence of inflammatory reaction in general or other adverse effects were observed in these studies. Decreases in neutrophils and protein (albumin) that were not considered adverse were seen in mice. As a compensatory response, myeloid hyperplasia in the bone marrow was inconsistently detected in some animals. The reason for the low neutrophil counts is unclear but may

be a mouse-specific effect of gantenerumab on neutrophils. Indeed, no such finding was observed in long-term nonclinical (murine and monkey) and clinical studies, and there have been no symptoms indicating immunosuppression in either species.

In cynomolgus monkeys, gantenerumab was well tolerated in repeat-dose IV toxicity studies of 13 and 26 weeks in duration (3, 10, and 20 mg/kg) and in SC toxicity studies of 13 weeks in duration (20 mg/kg) and 39 weeks in duration (up to 375 mg/kg). In the 26-week toxicity study, in which gantenerumab was administered once weekly, one male monkey in Group 2 (3 mg/kg) was found dead 24 hours after receiving the 26th dose (Day 177). The death was not considered to be related to gantenerumab treatment but rather to a bacterial infection detected on histopathology. There was no treatment-related effect on hematologic parameters (i.e., neutrophil counts) in studies in cynomolgus monkeys.

In the absence of any adverse treatment-related effect in the 39-week toxicity study, a no-observed-adverse-effect level of 375 mg/kg/wk was established, which correlated with a mean maximum concentration (C_{max}) of 2535 μg/mL (male and female animals combined) and a mean area under the concentration–time curve from Time 0 to 168 hours ($AUC_{0-168hr}$) of 386,000 μg • hr/mL (male and female animals combined).

Reproductive toxicity studies in transgenic PS2APP mice did not reveal an effect of gantenerumab on fertility, embryo–fetal, or post-natal development.

1.2.2 Clinical Studies

Gantenerumab has been investigated in *10* completed Phase I clinical studies: three single-ascending dose (SAD) studies (BN18726, JP22474, and BP30042) of healthy volunteers *and patients with mild to moderate AD*, two multiple-ascending dose (MAD) studies (NN19866 and JP22431) of patients with mild to moderate AD, and three bioavailability studies of healthy subjects (one comparing the IV and SC formulations of gantenerumab [Study WP22461], two comparing lyophilized and high-concentration liquid formulations of gantenerumab [Studies WP27951 and BP29113]). *In addition, a tolerability study comparing the pain between faster and slower SC administrations of gantenerumab has been completed (Study WP39322).*

In order to assess suitability of the G4 material for future Phase III studies, an extended analytical comparability program was conducted followed by the nonclinical studies. Since differences were observed in AUC, a human relative bioavailability study (WP40052) comparing G3 and G4 gantenerumab after SC administration *has also been* conducted.

A total of *543* subjects have participated in the Phase I studies; of these participants, *406* healthy volunteers and 101 patients with AD have received gantenerumab. Two Phase III studies designed to examine efficacy and safety of gantenerumab in patients with prodromal AD (Study WN25203) and mild AD (Study WN28745) have been

converted to OLE studies. The OLE studies examining the safety and tolerability of higher doses of gantenerumab in prodromal AD (Study WN25203) and mild AD (Study WN28745) are ongoing.

Results of relevant studies are summarized below. Refer to the Gantenerumab Investigator's Brochure for further information.

In addition, gantenerumab is being investigated in the Dominantly Inherited Alzheimer Network Trial, a Phase II/III study sponsored by the Washington University School of Medicine, examining the safety, tolerability, biomarker status, and efficacy of gantenerumab (as measured by cognition) in patients who are known to have an AD-causing mutation and are therefore at risk for developing AD dementia.

1.2.2.1 Study NN19866

In the MAD study (NN19866), a total of 60 patients (34 males and 26 females) diagnosed with mild to moderate probable AD received multiple IV doses of gantenerumab (doses ranging from 6 mg to 20 mg, 60 mg, and 200 mg) or placebo every 4 weeks (Q4W) for up to 7 months. Owing to amyloid-related imaging abnormalities (ARIAs), or ARIAs of "vasogenic edema" (ARIA-E) and of "hemosiderosis or microbleeds" (ARIA-H), on brain magnetic resonance imaging (MRI) scans that occurred in some patients after two to four doses of 200 mg of gantenerumab in Cohort 4 (200 mg IV Q4W gantenerumab [equivalent to 330 mg SC Q4W] or placebo), it was decided to terminate dosing for all patients on 9 June 2008. The findings resolved spontaneously within 1–4 months after discontinuation of gantenerumab and no patient required treatment.

1.2.2.1.1 Study NN19866: Pharmacodynamic Results in the NN19866-PET Substudy

In a positron emission tomography (PET) substudy of Study NN19866 (NN19866-PET), the effects of gantenerumab on amyloid load in the brain (defined as standardized uptake value ratio [SUVr] of a cortical composite volume of interest over mean cerebellum gray and using ^{11}C-PiB PET) were evaluated in 18 patients (4 in the placebo group, 8 in the 60-mg IV gantenerumab dose group, and 6 in the 200-mg IV gantenerumab dose group) after 6 months. A mean decrease of 14.9% from baseline was observed in the 200-mg gantenerumab dose group, while an increase was seen in the placebo group (mean, 20.9%), with relative stability compared with baseline in the 60-mg group (mean, 5.3%) (Ostrowitzki et al. 2012).

1.2.2.2 Study WN25203

Based on the results from Study NN19866 and from a relative bioavailability study WP27951, the doses of 105 mg SC Q4W (equivalent to 60 mg IV Q4W) and 225 mg SC Q4W (equivalent to 130 mg IV Q4W) were selected *for Study WN25203*.

Study WN25203 was initially designed as a Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy

of 105 mg and 225 mg of gantenerumab administered subcutaneously Q4W in prodromal AD after 2 years of treatment. Randomization was based on apolipoprotein E, allele ε4 (*APOE* ε4) status. Selection of gantenerumab doses was largely driven with the objective of reducing risk of MRI findings (in the context of the clinical understanding of ARIAs at the time of study design) and by pharmacodynamic (PD) results in the MAD study NN19866. Study WN25203 enrolled 799 patients, and 797 patients were treated (the safety-evaluable population). Following a planned interim futility analysis when approximately 50% of patients had completed 2 years of treatment), the study was declared futile and dosing with the originally selected doses (105 mg and 225 mg) was suspended in December 2014. The mean duration of double-blind treatment was 1.73 years.

Safety analyses confirmed ARIAs and injection-site reactions (ISRs) (associated with SC administration) as identified risks of gantenerumab (see Section 1.2.3 for more details). Approximately 90% of patients experienced at least one adverse event, with the incidence comparable between treatment arms. The incidence of serious adverse events was 19.5%, 17.3%, and 16.9% in the placebo, 105-mg gantenerumab, and 225-mg gantenerumab groups, respectively *(Ostrowitzki et al. 2017)*.

Subsequently, the trial has been converted into an OLE study evaluating doses of up to 1200 mg (see Section 1.3.1).

1.2.2.3 Study WN28745

Study WN28745 was initially designed as a Phase III, 2-year, double-blind, placebo-controlled, efficacy, and safety study of gantenerumab in approximately 1000 patients with mild AD. Patients randomized to receive gantenerumab were to follow a slow titration scheme independent of *APOE*-ε4 genotype, starting at 105 mg of SC gantenerumab Q4W for the first 24 weeks, with progression to 225 mg, based on acceptable results of the control MRI scan. The study enrolled 389 patients, *and 387 patients were treated. There were 108 patients also enrolled in a PET substudy of brain amyloid imaging (Study WN28745-PET).* Following the WN25203 futility analysis, study recruitment was stopped and the study was converted to an OLE study, evaluating the safety and tolerability of gantenerumab at higher doses (up to 1200 mg).

1.2.2.4 OLE Studies WN25203 and WN28745

Additional analyses of Study WN25203 results indicated that higher doses of gantenerumab may achieve clinically relevant effects on cognition and function (see Section 1.3.1). Thus, both Studies WN25203 and WN28745 were converted to OLE studies to provide participants, including those in the placebo group, the opportunity for treatment with higher doses of gantenerumab expected to have a clinically meaningful effect. Doses up to 1200 mg SC Q4W of G3 gantenerumab are being tested, using dosing regimens designed to minimize the risk of ARIAs and taking into account the *APOE* genotype and the previous double-blind treatment and dose.

As of *23 October* 2017, *383* patients had been enrolled in the OLE studies WN25203 and WN28745, with *349* patients exposed to G3 gantenerumab doses higher than 225 mg (i.e., more than the highest repeat dose previously tested in AD patients) and *260* patients having reached the OLE target 1200-mg dose. ISRs and ARIAs remain the identified risks for gantenerumab. Safety data and MRI findings *have been* monitored by *an* iDMC, which has not identified any new safety signal in these ongoing studies.

1.2.2.5 *Study WP40052*

A total of 114 healthy male and female subjects received a single dose of 600 mg of gantenerumab high concentration, liquid formulation (containing gantenerumab manufactured by either G3 or G4 process, N =57 in each treatment group). The results showed that the plasma exposure in terms of area under the concentration–time curve from Time 0 to infinity (AUC_{inf}) was approximately 1.18 fold higher after SC administration of material manufactured by G4 process compared with material manufactured by G3 process, whereas C_{max} was similar (1.05 fold higher after administration of G4 material). Single-dose SC administration of 600 mg of gantenerumab as G3 or G4 material was safe and well tolerated.

Refer to the Gantenerumab Investigator's Brochure for details on nonclinical and clinical studies.

1.2.3 Safety Overview

Nonclinical characterization of gantenerumab did not show *any* relevant safety findings. To date, ARIAs and injection-site reactions (ISRs) are the identified risks for gantenerumab. No differences between active and placebo groups have been observed in laboratory parameters, physical and neurological examinations, vital signs, or electrocardiogram (ECG) parameters.

Amyloid-Related Imaging Abnormalities

In the double-blind portion of Study WN25203 (prodromal AD), ARIA events were time, dose, and *APOE* ε4 allele status dependent. The incidence of ARIA-E was 0.8% in the placebo, 6.6% in the 105-mg gantenerumab, and 13.5% in the 225-mg gantenerumab groups. For ARIA-H, the incidence was 13.2% in the placebo, and 22.9% and 16.2% in the 105-mg and 225-mg gantenerumab treatment groups, respectively. The rates of new ARIA-E were highest between 3 and 6 months of treatment (3.8% and 7.5% in the 105-mg and 225-mg gantenerumab groups, respectively) and decreased substantially after the first year of treatment (incidence of up to 2.3% in the 225-mg gantenerumab group in approximately 2 years). The median MRI Barkhof grand total score (BGTS) (Barkhof et al. 2013) of these findings was 3. Five patients (1.8%) from the 105-mg gantenerumab arm and 6 patients (2.3%) from the 225-mg gantenerumab arm experienced symptoms related to ARIA findings. Overall, most ARIA events were asymptomatic, non-serious, and of mild severity, except one serious adverse event of "partial seizures." Otherwise, the most commonly reported symptom was "headaches."

Following the futility analysis for Study WN25203, recruitment of the Phase III study (WN28745) was stopped. From 389 randomized patients, 387 patients were dosed with double-blind treatment (safety population), 192 patients in the gantenerumab arm and 195 patients in the placebo arm. Treatment in the double-blind phase was discontinued in July 2017 (median double-blind treatment duration: 68 weeks) and consenting patients transitioned into OLE. As of 16 January 2018, the double-blind part of Study WN28745 is ongoing with a small number of patients still in the post-treatment follow-up phase.

In the double-blind part of Study WN28745, the frequency of ARIA-E was 1.5% and 11.5% in the placebo and gantenerumab group, respectively. The frequency of ARIA-H was 11.8% and 15.6% in the placebo and gantenerumab group, respectively. The median BGTS of ARIA-E was 3. Overall, most ARIA events were asymptomatic, with only 2 patients (1.0%) in the gantenerumab group reported as having experienced a symptom related to ARIA (a non-serious and mild dizziness, and a non-serious and moderate headache).

The WN25203 and WN28745 OLE studies are ongoing and consequently, data are still *accruing*. As of *23 October* 2017, *383* patients had been enrolled and *377* dosed; *349* patients had their dose uptitrated to doses higher than 225 mg, and *260* patients were dosed with at least one gantenerumab dosage of *1200* mg.

Of the *377* patients dosed, *350* patients had undergone at least *one* postbaseline MRI scan. *In the WN25203 OLE study, 32 out of 133 patients with a postbaseline scan (24.1*%) had new ARIA-E *(*median maximum BGTS *was 6.5). In the* WN28745 *OLE study, 61 out of 217 patients with a postbaseline scan (28.1%) had new ARIA-E (median maximum BGTS was 8.0).* Most ARIA-E cases were asymptomatic; associated symptoms were reported for *20 of 93* patients *who had ARIA-E (2 patients* exposed to 225 mg of gantenerumab, *4* to 450 mg, 2 to 600 mg, *4* to 900 mg, and *8* to 1200 mg). The most frequently reported symptoms included visual impairment, dizziness, confusion, headache, and worsening of memory. Of the*20* symptomatic cases, there were *five* serious events*: one case of confusion resulting in hospitalization, one case of a possible ischemic stroke, and three cases of seizure/epilepsy. In two of the epilepsy cases, the seizure/epilepsy resolved in the absence of any specific* treatment within 24 hours*. In the third case, the patient was given antiepileptic treatment (phenobarbital and phenytoin; phenytoin was subsequently replaced by lacosamide due to an orticarioid reaction). The patient also had several electroencephalograms that showed a reduction in epileptic discharge*.

Twenty-three patients had ARIA-H events only (i.e., without concomitant ARIA-E); no symptoms were reported.

Injection-Site Reactions

In *the double-blind part of* Study WN25203, the overall incidence of ISRs was 15.4%, with the majority of the events being of mild intensity and resolved spontaneously. The incidence of ISRs was 4.5%, 18.8%, and 23.1% in the placebo, 105-mg gantenerumab, and 225-mg gantenerumab groups, respectively.

In the double-blind part of Study WN28745, the incidence of ISRs was 1.0% and 8.9% in the placebo and gantenerumab group, respectively. All ISRs were non-serious and mild in intensity; the vast majority resolved without treatment. The most common signs and symptoms included injection site erythema and injection site itching. No patients discontinued study treatment due to ISR.

As of *23 October* 2017, ISRs were reported in *93* patients (*24.7*%) across the OLE studies WN25203 and WN28745 and *9* patients received treatment for these events. The most common symptom was localized erythema. None of the events were serious or led to study drug discontinuation. One patient reported a severe event, injection-site pain after receiving a 600-mg dose by means of a pump, resulting in modification *of* uptitration. Most of ISRs were mild, resolved without treatment, and led to dose modification in only one case.

The Sponsor performs regular reviews of *OLE Studies WN25203 and WN28745* data and, to date has not identified any new or unexpected safety findings. In addition, an independent Data Monitoring Committee (iDMC) *reviewed* data at quarterly intervals and the conclusion of the last meeting (held on *15 December* 2017) was that the studies continue without modifications.

For safety data from all studies, refer to the Gantenerumab Investigator's Brochure.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Currently, approved therapies for AD focus on symptomatic approaches that target synaptic function and cognitive enhancement (Cummings 2004). However, the amyloid hypothesis suggests that overproduction of Aβ or failure to effectively clear this peptide contributes to AD (Selkoe and Hardy 2016) and that accumulation of Aβ peptides is one factor contributing to AD progression (Sun et al. 2015). Thus, the targeting of Aβ and subsequent displacement of Aβ from the brain is a rational approach to modify AD progression.

Despite compelling results in AD animal models (Wisniewski and Goñi 2014), clinical success with passive immunization targeting brain amyloid in global Phase III trials remains an unachieved goal. It has been suggested that lack of sufficient target engagement of anti-amyloid antibodies has been a factor in the failure of these Phase III studies (Cummings et al. 2016). An important advancement for therapies targeting aggregated amyloid was provided based on data from the Phase Ib PRIME study of aducanumab (Biogen) (Sevigny et al. 2016).

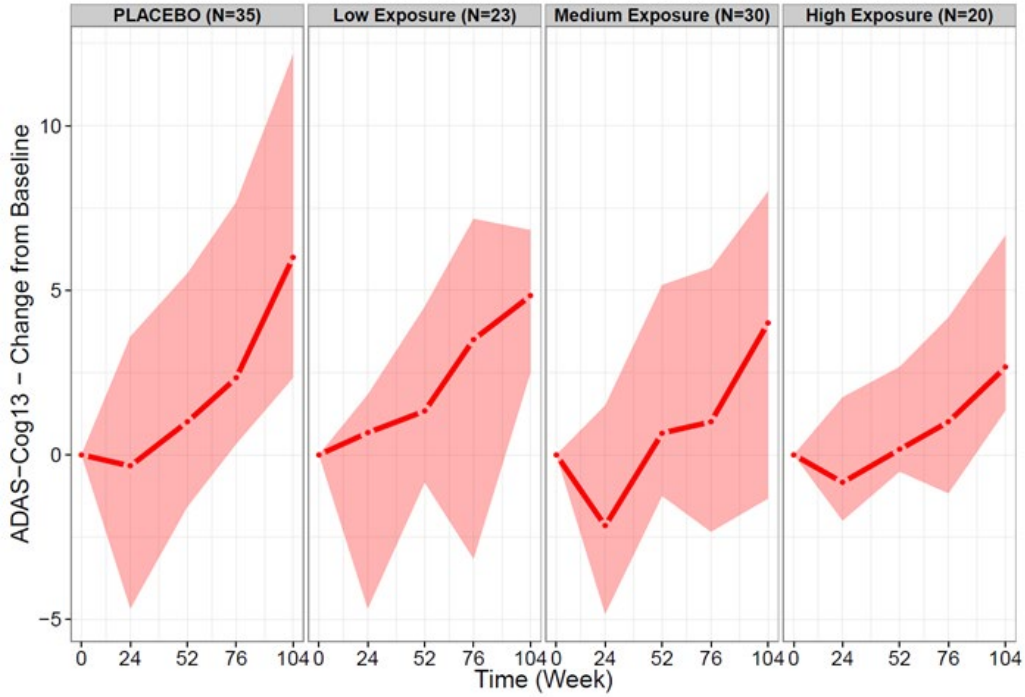
Aducanumab is a fully human IgG1 monoclonal antibody with similar PK and PD properties as gantenerumab that binds to aggregated target fibrillary and oligomeric forms of Aβ through microglia-mediated clearance of amyloid plaques (Sevigny et al. 2016). The results from the PRIME study showed that monthly IV injections of aducanumab for 1 year led to a dose- and time-dependent reduction of amyloid plaques in the brain. In addition, in patients with *early* (prodromal to mild) AD, a slowing of clinical decline, as measured on the Clinical Dementia Rating–Sum of Boxes (CDR-SOB) and Mini-Mental State Examination (MMSE) scores, has also been observed providing support to the hypothesis that Aβ plaque reduction confers clinical benefit.

1.3.1 Study Rationale

The results of the preplanned futility analysis of data from approximately 300 patients in Study WN25203 revealed the low likelihood for trial success with the original doses studied. Indeed, no significant differences were observed on any cognitive or functional measures (i.e., CDR-SOB, MMSE, Alzheimer Disease Assessment Scale–Cognition, Subscale 13 [ADAS-Cog13], and Functional Activities Questionnaire [FAQ]) or in a subgroup analysis of baseline characteristics (demographics, cognitive, CSF biomarkers, disease severity, or *APOE* ε4 allele status). Additional post-hoc analyses indicated that the overall rate of clinical decline was lower than expected for this study population (and with higher-than-expected proportion of "slow progressors") and strongly suggested that the doses studied in Study WN25203 (105 and 225 mg) were subtherapeutic and that a higher gantenerumab dose may have a clinically relevant effect *(Ostrowitzki et al. 2017)*.

Results of the post-hoc analyses of patients who were predicted to be progressors using a model derived from the Alzheimer's Disease Neuroimaging Initiative data (Delor et al. 2013) showed a drug concentration-dependent effect on clinical decline present for the ADAS-Cog13, MMSE, and Cambridge Neuropsychological Test Automated Battery results. Figure 1 displays the effects on increasing plasma gantenerumab concentrations (three concentration groups) on ADAS-Cog13 decline over the 2-year study. Greater concentrations of gantenerumab were associated with less clinical decline.

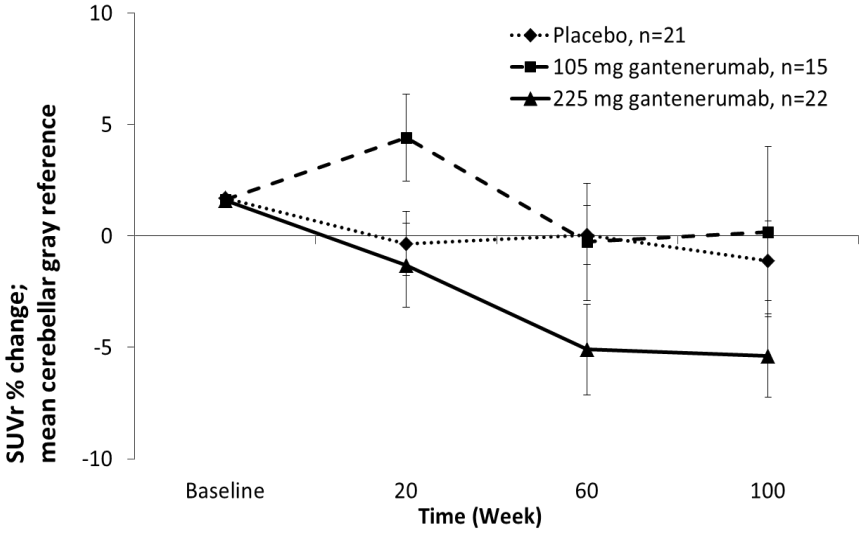
Figure 1 ADAS-Cog13 Treatment Response by Plasma Concentration: Two-Year Completing Fast Progressors in Study WN25203



ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13.
Notes: low exposure = 1.48–5 μg/mL; medium exposure = 5–10 μg/mL; high exposure = 10–26.68 μg/mL. Line = median; shaded = 50% observations.

Furthermore, a PET substudy of Study WN25203 using florbetapir F 18 confirmed a reduction in brain amyloid in gantenerumab-treated patients in a larger, less-impaired patient sample compared with Study NN19866, which had also demonstrated reduced accumulation of brain amyloid. Time-dependent reductions in SUVr were observed in patients treated with 225 mg of gantenerumab compared with placebo using the composite cortical SUVr and reference region of mean cerebellar gray. Week 100 results showed the mean percent change from baseline in SUVr was −1.09%, 0.72%, and −4.82% in the placebo, 105-mg gantenerumab, and 225-mg gantenerumab groups, respectively (see Figure 2). A small number of patients (n = 8) continued to receive 225 mg of gantenerumab for approximately 3 years (Week 156). Analysis suggested that the effect on SUVr reduction was continuous over time because SUVr reductions observed with the 225-mg dose of gantenerumab relative to placebo increased with the duration of long-term exposure, suggesting a sustained effect with continued exposure.

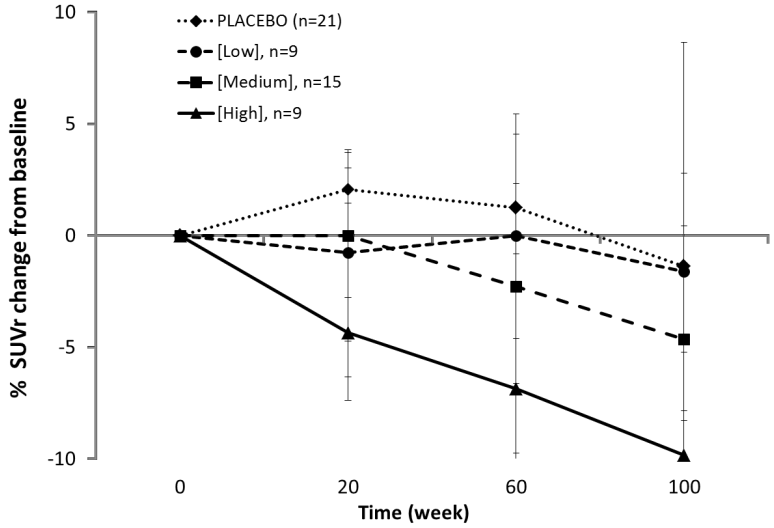
Figure 2 Mean Percent Change from Baseline in Composite Amyloid PET SUVr by Cerebellum Gray Reference: Study WN25203, PET Substudy



PET = positron emission tomography; SUVr = standardized uptake value ratio.

In Study WN25203, a concentration-based analysis of the PET results showed a clear response relationship between gantenerumab concentration in plasma and SUVr reduction, with greater mean concentrations resulting in greater amyloid clearance. As depicted in Figure 3, small changes in SUVr were present in the placebo and 1.9–5-μg/mL gantenerumab groups, whereas the higher concentration groups (5–10 μg/mL gantenerumab and 10–20.72 μg/mL gantenerumab) displayed SUVr reductions of up to 5% and 10%, respectively. These analyses indicate that higher doses may produce greater Aβ clearance that may translate into greater clinical effect.

Figure 3 Median Changes over Time in Concentration-Dependent PET SUVr by Gantenerumab Serum Concentration and Cerebellum Gray Reference: Study WN25203, PET Substudy



PET = positron emission tomography; SUVr = standardized uptake value ratio.
Note: low = 1.9–5 μg/mL; medium = 5–10 μg/mL; high = 10–20.7 μg/mL.

In addition, CSF analyses performed in Study WN25203 showed dose-dependent reductions in both CSF tau species (total tau [t-tau] and phosphorylated tau [p-tau]) in patients receiving gantenerumab compared with placebo. No change in CSF $A\beta_{42}$ was present over the 2-year period, as expected, given the mechanism of action of gantenerumab that targets fibrillar over monomeric Aβ.

Overall, these findings indicate the presence of clinical and biological effects of gantenerumab in subjects who had the highest exposure. In overall study population, results from the futility analysis of Study WN25203 indicated that the likelihood of the 225-mg dose of gantenerumab achieving a clinical effect was very low. These findings indicate that higher doses are required to achieve a clinical effect associated with the biological activity indicated by the amyloid and tau biomarker findings in Study WN25203. As a result, the decision was made to convert Studies WN25203 and WN28745 into OLE studies to give all patients the opportunity to receive higher doses of gantenerumab and to assess the safety of higher doses.

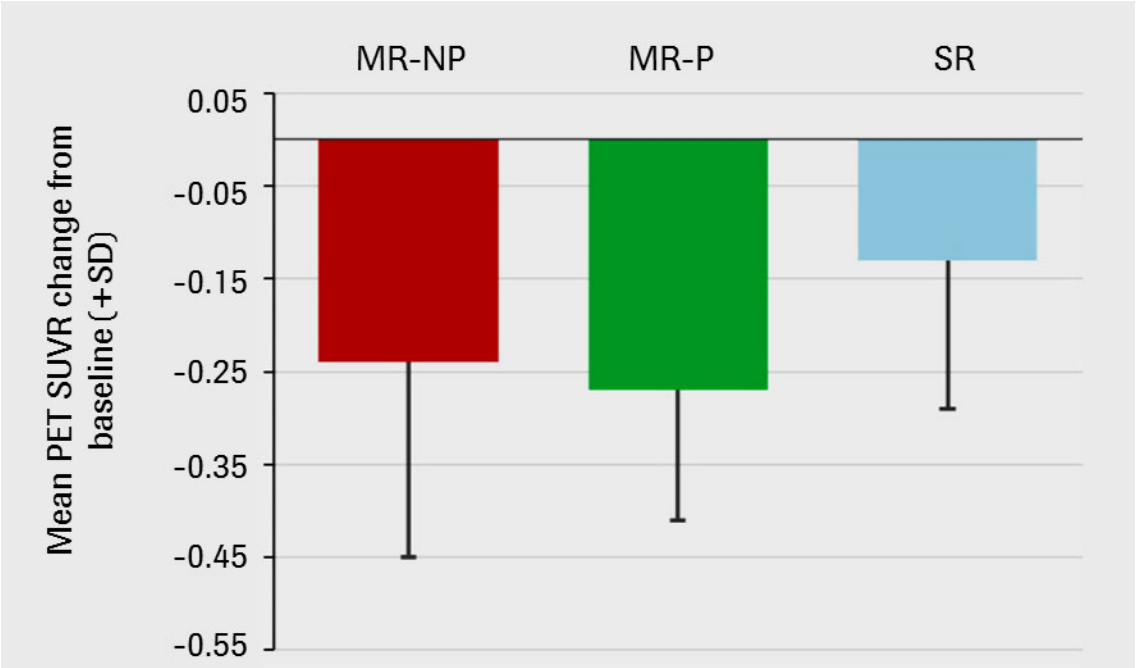
Additional support for using higher doses of gantenerumab comes from PK-PD models. Based on the established similarities between gantenerumab and aducanumab *(see* Section 1.3*)*, a model characterizing the relationship between *plasma* drug concentration (PK) and PET response (i.e., the PD effect on amyloid load in the brain) was derived from both gantenerumab study WN25203 data and aducanumab PRIME data to determine the target dose of gantenerumab for the OLE studies (for further details see

Appendix 4). In the OLE studies, the 1200-mg dose of SC gantenerumab Q4W is predicted to achieve plasma levels comparable to 10 mg/kg of IV aducanumab Q4W and to be associated with a comparable (~20%) amyloid brain reduction, which, in the case of aducanumab, was associated with a statistically significant clinical effect after 1 year of treatment. In order to minimize the occurrence of ARIA-E while achieving the target dose within a reasonable time frame, several titration schedules have been explored in the WN25205 OLE and WN8745 OLE studies.

Gantenerumab PK-PET models of amyloid reduction have been confirmed by PET data from the OLE studies. There were 85 patients from the OLE studies included in an amyloid PET substudy using florbetapir F 18 (Amyvid™). As of 31 August 2017, 40 patients treated with a dose of 900-mg to 1200-mg gantenerumab for ⩾6 months had a PET scan at Week 52 of the OLE studies. Patients were divided into three groups for analyses purposes, based on the study and on the double-blind treatment prior to switching to open-label gantenerumab and dose increase: Study WN28745 placebo (Marguerite RoAD non-pretreated [MR-NP], in the placebo arm during the double-blind part, N=14), Study WN28745 pretreated (Marguerite RoAD pretreated [MR-P], active arm during the double-blind part, low-dose gantenerumab, ⩽ 225 mg, N=17), and Study WN25203 (SCarlet RoAD [SR], off-treatment for approximately 78 weeks median, N=9). Across the three groups, there was a 7%–16% reduction in PET composite SUVr from baseline using the pre-specified cerebellar grey reference region, which was a 2- to 3-fold increase in the reduction observed in the double-blind WN25203-PET substudy with 225-mg gantenerumab after 2 years of treatment and in a good alignment with the PK-PET efficacy model (Figure 4). Also, approximately one-third of patients in the OLE PET substudy fell below the quantitative amyloid positivity threshold after 1-year titration and with 6–9 months at higher doses (⩾ 900 mg). PET scans with a quantitative amyloid level below threshold were shown to be concordant with a negative visual amyloid PET read and consistent with sparse to no neuritic amyloid plaques in histopathology verified studies (Joshi et al. 2012). Based on this data, it is expected that after 2 years of treatment on higher-dose gantenerumab, most patients may have an amyloid burden within the range typical of a healthy age-matched population. Taken together, these results strongly confirm the gantenerumab mechanism of action and support selection of target dose for Study WN39658 (see Section 1.2.3).

Figure 4 shows the reduction of brain amyloid PET SUVr in patients exposed to at least 900 mg for 6–9 months in the WN25203 (SCarlet RoAD) and WN28745 (Marguerite RoAD) OLE studies. Analysis is stratified by patients from the Marguerite RoAD non-pretreated (MR-NP) arm in the double-blind study, Marguerite RoAD pretreated (MR-P) arm, and the SCarlet RoAD study (SR).

Figure 4 Reduction of Brain Amyloid PET SUVr in Patients Exposed to at Least 900 mg for 6–9 Months in WN25203 (SCarlet RoAD) and WN28745 (Marguerite RoAD) Open-Label Extension Studies



MR-NP =Marguerite RoAD (WN28745) non-pretreated, N=14; MR-P =Marguerite RoAD (WN28745) pretreated, N=17; PET =positron emission tomography; SD = standard deviation; SR =Scarlet RoAD (WN25203, N=9); SUVr =standardized uptake value ratio.

1.3.2 *Rationale for Dosing Strategy*

As indicated in Section 1.3.1, the target dose of 1200 mg G3 material administered in the WN25203 and WN28745 OLE studies has been identified based on PK-PD modeling and simulations (details about the model are presented in Appendix 4) and is predicted to lead to an amyloid PET reduction similar to 10 mg/kg IV aducanumab Q4W. The OLE PET data have shown been consistent with these predictions.

In the OLE studies WN25203 and WN28745, patients were allocated to different titration schedules (two schedules in Study WN25203 and four schedules in Study WN28745) according to their *APOE* allele status and treatment arm during the double-blind period of the parent studies. These titration schedules were implemented in order to mitigate the risk of ARIA events. A*n ARIA-E hazard model* was first developed *on* bapineuzemab *data* (Hutmacher et al. 2013). This model, which includes drug concentrations, time since first dose, and *APOE* ε4 allele status, was applied to the double-blind results in Study WN25203; the model was then tested on publicly available aducanumab data from the PRIME study and were used to predict the incidence of ARIA-E events with a high degree of accuracy, including the observed ARIA-E rate differences across *APOE* ε4 allele groups.

Recently, the ARIA-E hazard model has been updated with observations from the WN25203 and WN28745 OLE trials using higher doses of gantenerumab (see Appendix 5).

*Using the validated PK-PET and ARIA-E hazard model, m*ultiple titration options have been simulated, including separate simulations for *APOE* ε4 allele carriers and non-carriers. Two different types of titration schedules, reflecting the different risk for ARIA events between *APOE* ε4 allele carriers and non-carriers were considered. Although an *APOE* ε4 genotype–based titration regimen could permit *APOE* ε4 non-carriers to achieve the target dose more quickly, an option with a single, slower titration schedule for all patients is favored as it provides an overall lower risk for ARIA. Given the chronic and gradually progressive nature of AD, the favored option is a single, slow titration schedule for all patients because it is simpler for clinicians, less prone to error, and does not require *APOE* genotyping before the initiation of treatment.

Thus, based on the information from the WN25203 and WN28745 OLE studies, in which gantenerumab (manufactured with G3 process) up to 1200 mg Q4W was assessed and shown to be safe for APOE ε4 allele carriers and non-carriers, and based on the internally developed PK-PD models, the following dosing regimen for Study WN39658 was selected: 150 mg Q4W for 3 months, then 300 mg Q4W for 3 months, and then 600 mg Q4W for 3 months, followed by 600 mg Q2W until the end of the study. The switch to a Q2W administration schedule allows patients to decrease the number of SC administrations in the abdomen per visit.

The PK-PD models referenced above were developed based on information from the G3 material and were used to establish the initial dosing regimen for this study. As indicated previously, gantenerumab drug substance manufacturing process was optimized from G3 to G4, and a relative bioavailability study (WP40052) assessed the pharmacokinetic difference between the G3 and G4 material in humans.

The results of this relative bioavailability study (WP40052) show that the AUC_{inf} is approximately 1.18 fold and the C_{max} is approximately 1.05 fold higher after administration of G4 compared with G3. As AUC is considered the driver of the treatment effect, the conversion factor of 1.18 from the G3 to G4 material has been based on the AUC_{inf}. The association between microglial-driven removal of aggregated brain amyloid and AUC has been shown in preclinical experiments and clinical studies. In addition, as gantenerumab exhibits linear pharmacokinetics, the AUC_{inf} after single dose reflects the steady state exposure (AUC_{tau}) after multiple doses.

Based on the above rationale and the fact that gantenerumab manufactured with G4 process was safe and well tolerated, the G3 dosing regimen has been converted into the following G4 dosing regimen for the WN39658 study: 120 mg Q4W for 3 months, then 255 mg Q4W for 3 months, and then 510 mg Q4W for 3months, followed by 510 mg Q2W until the end of the study. This schedule enables titration to target dose within

9 months (see Table 1), with predicted overall ARIA-E rate of approximately 26% based on the current ARIA-E hazard model. The low starting doses and gradual increase in dosing (i.e., slow titration schedule) are expected to reduce the risk of ARIA-E for both APOE carriers and non-carriers. An MRI scan, confirming the absence of ARIA-E findings, will be required prior to each dose increase.

Table 1 Proposed Dose and Titration Regimen for Phase III Studies

Month	1	2	3	4	5	6	7	8	9	10
Dosing frequency	*Q4W*	*Q4W*	*Q4W*	*Q4W*	*Q4W*	*Q4W*	*Q4W*	*Q4W*	*Q4W*	*Q2W*
Dose (mg)	*120*	*120*	*120*	*255*	*255*	*255*	*510*	*510*	*510*	*510*

1.3.3 Risk-Mitigation Measures for ARIA Findings

ARIA is the most significant adverse event reported in therapies against aggregated forms of Aβ. These findings appear to be dose, time, and *APOE* ε4 allele dependent (Piazza and Winblad 2016).

The mechanism underlying the development of ARIA-E and ARIA-H during anti-amyloid treatment is unknown. Because antibodies target removal of Aβ from both the parenchyma and cerebral vasculature, vessels with preexisting amyloid vascular pathology might become transiently more susceptible to leakage of vascular contents. This pathology results in ARIA-E if the leakage consists of proteinaceous fluid and in ARIA-H if the leakage consists of blood products (Sperling et al. 2012).

*Thus, a*n anti-Aβ therapy that effectively maintains vascular β-amyloid clearance would allow *vascular remodeling and may,* with time, *decrease* the risk of such extravasation events *(Sperling et al. 2012)*. This is consistent with experience in previous and ongoing studies and with reported data from the long-term extension study of aducanumab treatment (Viglietta et al. 2016).

Previous and ongoing studies with gantenerumab showed that ARIAs are manageable with MRI monitoring and dose intervention algorithms (i.e., temporary study drug interruption or temporary suspension of uptitration) and that these events are mostly asymptomatic. Recent data from the long-term extension of the PRIME study (aducanumab) suggested also that a titration up to 10 mg/kg (predicted to be comparable to 1200 mg of SC *Q4W* G3 gantenerumab (or *510* mg of *SC Q2W* G4 gantenerumab) per the *PK-PD* model (see Appendix 4) may reduce the incidence of ARIA-E compared with higher fixed dosing (Viglietta et al. 2016).

In Study WN39658, imaging-related criteria will be used to exclude patients with clinically important cerebral vascular disease at baseline, as well as ARIA-related lesions. A slow titration schedule will be implemented to reach the target dose, and MRI monitoring will be conducted during the study at regular intervals (see Appendix 1, *and*

Tables 1 and 2, for the schedule of activities for the uptitration and MRI schedules). An MRI scan documenting the absence of ARIA-E findings will be required prior to each dose increase. If ARIA findings occur, more intense MRI monitoring, dose adjustments, temporary dose holding, or permanent discontinuation will be implemented according to an ARIA-related dose-adjustment plan, described in Section *5.1.3*. Safety findings (including unblinded individual patient and aggregate data) will be reviewed on a regular basis by the iDMC.

1.3.4 Risk to Patients without Alzheimer's Disease Pathology

Owing to the rigorous screening procedures in this study, including measurement of the CSF tau to $A\beta_{42}$ ratio and/or amyloid PET scan, it is *anticipated* that only patients with AD pathology will be enrolled. In the event that a patient without amyloid pathology is enrolled, no additional risk is expected. However, such patients may still experience side effects related to administration of gantenerumab (e.g., ISRs and development of anti-drug antibodies [ADAs]).

1.3.5 Overall Benefit–Risk Summary

Overall, the benefit–risk assessment of gantenerumab is based on the following:

- Gantenerumab *has* shown evidence of reducing amyloid plaques (i.e., observed evidence of brain amyloid reduction*)* and, thus, shows potential benefit in slowing the progression of AD.
- Findings from the WN25203 and aducanumab PRIME studies provide additional support for the hypothesis that anti-amyloid treatment may be associated with a beneficial clinical effect.
- Results from the double-blind portion of Study WN25203, as well as from the OLE studies WN25203 and WN28745, showed that ARIA findings are mostly asymptomatic, non-serious, of mild severity*,* and do not require permanent cessation of treatment*. ARIAs are manageable with MRI monitoring and dose intervention algorithms, as detailed in Section 5.1.3.*
- *No new safety signal has been identified in the d*ata from the ongoing OLE studies *with* doses of up to 1200 mg *Q4W G3 material. These data support the administration of the target dose of 510 mg Q2W G4 material to both ApoE ε4 carriers and non-carriers in the WN39658 study.*

Thus, the anticipated benefit–risk profile of gantenerumab supports clinical trials with higher doses in the population with *early (*prodromal to mild*)* AD.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of gantenerumab compared with placebo in patients with *early (*prodromal to mild*)* AD. Specific objectives and corresponding endpoints for the study are outlined in Table 2.

Table 2 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of gantenerumab administered by SC injection compared with placebo	• The change from baseline (Day 1) to Week 104 in global outcome, as measured by the CDR-SOB
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo on cognition and function	The change from baseline to Week 104 in cognition and/or function, as measured by: • MMSE total score • ADAS-*Cog11 and* ADAS-Cog13 • Verbal Fluency Task • *Coding* • FAQ • ADCS-ADL total score *and instrumental score*
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo	The change from baseline to Week 104 in the following: • Time to clinically evident decline, defined as an increase of ≥2.0 in CDR-SOB subscore or ≥1 in at least four items of the FAQ • *Severity*, as assessed by the CDR Global Score • Function, as assessed by the CDR function subscore • Dependence level, as derived from the ADCS-ADL score • Cognition, as measured by the CDR cognition subscore • Health-related quality of life, as assessed by the QoL-AD scale • Behavioral and *neuropsychiatric* symptoms of AD, as measured by the NPI-Q • Study partner burden, as assessed by the ZCI-AD scale • Elements of resource utilization, as assessed by the RUD-Lite • Health outcomes in patient and study partner, as measured by EQ-5D questionnaire

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

Table 2 Objectives and Corresponding Endpoints (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of gantenerumab compared with placebo	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Presence of ADAs during the study relative to the presence of ADAs at baseline
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the PK profile of gantenerumab	• Plasma concentration of gantenerumab (administered subcutaneously) at specified timepoints
Pharmacodynamic Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo in patients with *early (*prodromal to mild*)* Alzheimer's disease	• Change from baseline in brain amyloid load, as measured by amyloid PET scan in a subset of patients • Change from baseline in brain tau load, as measured by tau PET scan in a subset of patients • Change from baseline in cerebral spinal fluid markers of disease in a subset of patients, including, but not limited to, $A\beta_{1-42}$, total tau, and phosphorylated tau • MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all patients
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo in patients with *early (*prodromal to mild*)* Alzheimer's disease	Plasma pharmacodynamic biomarkers Change from baseline to Week 104 in functional brain connectivity, as measured by resting-state functional MRI (where available) Change from baseline to Week 104 in *integrity of white matter*, as measured by DTI-MRI (where available)

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of gantenerumab in patients with *early* (prodromal to mild) AD.

The planned number of patients for the global enrollment phase for the study is approximately *760* patients: randomized in a 1:1 ratio to receive gantenerumab and placebo (*380* patients randomized to gantenerumab and *380* randomized to placebo). To maintain a balanced number of patients enrolled in each treatment arm and to ensure that the arms are comparable, randomization will be stratified by stage of disease (prodromal AD vs. mild AD), APOE allele status (presence vs. absence of the ε4 allele), use of AD medication (presence vs. absent), geographic region (*Western Europe vs. Rest of the World vs. North America*) and participation in longitudinal amyloid *and tau* PET *substudies*. Approximately *175* centers in approximately *15* countries worldwide will participate in this study.

Patients will be selected on the basis of clinical diagnosis of probable AD (according to the National Institute on Aging/Alzheimer's Association [NIA/AA] diagnostic criteria and guidelines for AD; see Appendix 2) (McKhann et al. 2011) or prodromal AD (according to the NIA/AA diagnostic criteria and guidelines for mild cognitive impairment (MCI) due to AD; see Appendix 3) (Albert et al. 2011). *The aim of the study is to recruit approximately 50% of the participants with prodromal AD.*

Eligible patients will be 50–90 years old, inclusive, must show evidence of β-amyloid pathology as indicated by the CSF tau to Aβ42 ratio (CSF-enrolled patients) or positive amyloid PET scan by visual read (PET-enrolled patients), and meet eligibility criteria as detailed in Section 4.1.

The study will consist of a screening period of up to *12* weeks in length following the signing of informed consent. *Sites also have* the option to prescreen patients on the Free and Cued Selective Reminding Test (FCSRT) *and MMSE*. Patients must sign a separate Informed Consent Form before administration of *these tests* if used for prescreening. If the results confirm a patient's eligibility, then the FCSRT *and MMSE* will not have to be completed again during the screening period as long as the test has been done within 12 weeks prior the baseline.

Eligible patients will then undergo baseline visit assessments (Day 1) prior to receiving the first dose of blinded study drug (gantenerumab or placebo). Patients will continue in the double-blind treatment period for 104 weeks. Visits and study drug administration will occur Q4W until patients reach the *target dose*, which will be *510* mg Q2W. After the last dose of study drug (Week 102), final efficacy and safety assessments will be

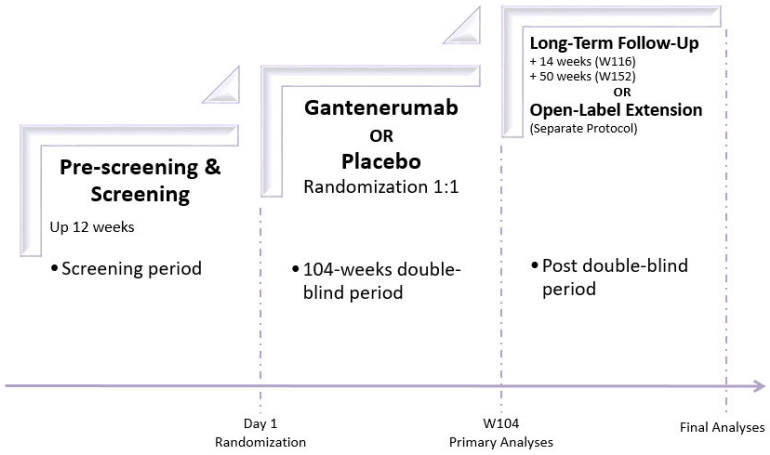
performed 2 weeks later (Week 104). Patients may then enroll in *an* OLE study *if eligible*. Patients who do not enter the OLE study will have additional follow-up visits at 14 and 50 weeks after the last dose for safety and limited efficacy assessments (Weeks 116 and 152, respectively). *Patients who prematurely discontinue treatment will continue in the double-blind treatment period and will be asked to return for collection of safety and limited efficacy data (see Section 4.7.1).*

Patients will undergo brain MRI examinations for safety monitoring and longitudinal changes in brain structure. MRI scans will be read by a central MRI reader (for more details regarding imaging-related criteria, see Section 4.1.2.2). Patients will also undergo standard tests to monitor safety (blood tests, ECG), as well as the Columbia–Suicide Severity Rating Scale (C-SSRS) to monitor for suicidality, tests for cognition, function, and quality-of-life (QoL) status. Blood samples for the assessment of PK samples, PD biomarkers, and anti-drug antibodies will be obtained from all patients.

The incidence and nature of adverse events, serious adverse events, ARIA-E and ARIA-H, adverse events of special interest, ECGs, and laboratory abnormalities will be assessed on a regular basis by an unblinded iDMC.

An overview of the study design is provided in Figure 5. The schedule of activities provided in Appendix 1.

Figure 5 Overall Study Design



W = week.

The study consists of three distinct periods:

- Screening *(including an optional prescreening)*: The screening period may last up to *12* weeks for each eligible patient.
- Double-blind treatment period: After screening, patients who meet all eligibility criteria will be randomly assigned to one of two arms (gantenerumab or placebo) in a 1:1 ratio. Following baseline assessments, each patient will receive a minimum of nine SC Q4W administrations of study drug (uptitration period), followed by up to 34 SC Q2W administrations of study drug in the 104-week, double-blind treatment period. The last dose of study drug will be administered at Week 102. At the end of the double-blind treatment period, all participants will undergo a Week 104 visit in order to collect data for the primary analyses.
- Post–double-blind treatment period: After the Week 104 visit, patients will be asked to come back for the long-term follow-up visits or to continue in the OLE.

  Long-term follow-up: Long-term follow-up will consist of a 50-week follow-up period with evaluations at Weeks 14 and 50 after completion of study drug administration or early termination for patients who do not enter the OLE.

  OLE study: All eligible patients will have the opportunity to enter an OLE study (details will be provided in a separate protocol).

For the schedule of activities at each visit, see Appendix 1, Tables 1 and 2.

China Enrollment Plan

Based on historical data, patient recruitment are expected to take longer in China; therefore, a specific China enrollment plan has been established. Thus, if at least 1 patient is enrolled *at sites* in *mainland* China*, Hong Kong, and Taiwan that are recognized by the China Food and Drug Administration (CFDA)* during the global enrollment phase, additional patients may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. All patients enrolled *at CFDA-recognized sites* in the global enrollment *phase* will be included in the primary analysis.

3.1.2 Substudies

The substudies associated with Study WN39658 will be described in separate protocols, and patients consenting to enroll in these substudies will be asked to sign the associated Informed Consent Forms.

3.1.3 Data Monitoring Committee

The iDMC will evaluate patient safety and efficacy on a regular basis. In addition to the data defined in the iDMC Charter (e.g., the incidence and nature of adverse events, serious adverse events, and adverse events of special interest, ARIA-E and ARIA-H), the iDMC will review all necessary cumulative data at regular intervals during the study, including efficacy when needed. It is anticipated that these assessments will occur approximately every 3 months. At the time of each review, the iDMC will make

appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, the treatment regimen should be modified, the protocol should be amended, enrollment should be held pending further safety evaluations). The iDMC will also evaluate planned *or unplanned* interim analyses for efficacy or futility (see Section 6.7.1).

Decisions will be made in consideration of the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities will be detailed in the iDMC Charter.

Final decisions will rest with the Sponsor.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for safety analyses or safety follow-up is received for the last patient, whichever occurs later.

The study will consist of a screening period of up to 12 weeks *(*including the optional prescreening period) for each eligible patient who signs the Informed Consent Form and agrees to participate, followed by a double-blind treatment period of 102 weeks of study drug treatment plus a visit 2 weeks after the last dose (Week 104), and followed by the post–double-blind treatment period of two follow-up visits at 14 and 50 weeks after the last dose (Weeks 116 and 152, respectively). Thus, for a patient not entering the OLE, the maximum length of study is approximately *164 weeks*.

3.3 RATIONALE FOR STUDY DESIGN

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of gantenerumab in patients with *early (*prodromal to mild*)* AD, increased amyloid burden (defined according to CSF or PET criteria), and clinical symptoms.

3.3.1 Rationale for Patient Population

As the accumulation of Aβ brain amyloid begins before the onset of AD dementia, it is reasonable to postulate that the benefit of anti-amyloid therapy may be greater if initiated at an early stage of the disease. For this reason, Roche has focused clinical development of gantenerumab on *early (*prodromal to mild*)* AD.

Patients in this study are required to meet standard research criteria for mild AD (according to the NIA/AA research criteria and guidelines for AD; see Appendix 2) or prodromal AD (according to the NIA/AA research criteria and guidelines for MCI due to AD; see Appendix 3). Note that the terms “prodromal AD” and “MCI due to AD” are considered to refer to the same population in this study and are defined according to

NIA/AA research criteria and guidelines for MCI due to AD. Thus, patients with prodromal AD will present with documented objective evidence of deficit in one cognitive domain. Patients with mild AD must present with documented deficits in at least two cognitive domains and evidence of functional decline. Overall, the population will have an MMSE between 22 and 30 (inclusive) points and a CDR global score (CDR-GS) of 0.5 or 1.0. The MMSE score provides evidence of no more than mild disease severity and the CDR-GS score indicates that the patients have prodromal AD or cognitive and functional deficits consistent with mild AD. *The aim of the study is to recruit approximately 50% of the participants with prodromal AD.*

Gantenerumab is an antibody that targets Aβ. Thus, the study population should have documented evidence of amyloid pathology. This patient selection approach is consistent with the NIA/AA research diagnostic criteria and guidelines for AD as well as with the Qualification Opinion from the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use on the use of CSF biomarkers for enrichment of trials in mild to moderate AD dementia (2012), and the U.S. Food and Drug Administration (FDA's) draft guidance for early AD (2013). Although the FDA's guidance refers to the early stage of AD in which individuals present with clinical MCI, biomarkers of amyloid pathology are expected to add value to patient selection in mild AD studies, especially for anti-amyloid treatments (McKhann et al. 2011; Dubois et al. 2014, 2016). Biomarker enrichment is important for anti-amyloid therapy clinical trials because some results of early trials have demonstrated that approximately 20% patients who are enrolled in trials based on a clinical diagnosis of AD alone may not have underlying amyloid pathology as assessed by amyloid PET (Doody et al. 2014; Salloway et al. 2014).

For enrollment in this study, biomarker evidence of β-amyloid deposition will be assessed either by a centralized visual assessment of PET amyloid imaging, using one of the three *following* amyloid PET imaging tracers (Vizamyl™, Neuraceq™, and Amyvid™ according to country and site availability) or by the CSF tau to $A\beta_{42}$ ratio (using a prespecified cutoff and the Roche Diagnostics Elecsys immunoassay).

Both methods (CSF and PET) are established approaches to identify Aβ accumulation in the brain in vivo (Pannee et al. 2016; Vos et al. 2016) and both have been used in research and in clinical practice. There is also emerging evidence that indicates consistency between PET amyloid imaging and CSF biomarkers. Indeed, in biomarker research studies, concordance between amyloid PET and the combination of CSF $A\beta_{1-42}$ with t-tau has been shown to be very high with properly controlled CSF methodologies (EMA 2012).

To enrich for *patients who are* more likely to decline over the 2-year trial, all patients have to demonstrate amnestic deficits as measured by the FCSRT's total free recall score and cueing index (Sarazin et al. 2007). The use of the FCSRT to support a hippocampal-related memory deficit (Buschke 1984; Grober and Buschke 1987) has

been recommended by the International Working Group (IWG-1; Dubois et al. 2007, 2010). Indeed, the core clinical symptom of AD is significant and progressive episodic memory impairment. Memory impairments because of AD are known to be hippocampal dependent and are thought to be characterized by a deficit in recall, which is often not recovered with cueing.

The FCSRT is a cued recall test that uses controlled encoding to ensure that impaired recall and cueing results are due to memory impairment and are not a failure at encoding (e.g., by means of attentional impairment). The FCSRT has demonstrated high sensitivity and specificity in differentiating patients with AD from both healthy controls and patients with other forms of dementia (Grober et al. 2008, 2010). More recently, the choice of the FCSRT as a valid clinical marker for typical prodromal AD (amnestic MCI) has been endorsed by the IWG-2 (Dubois et al. 2014) and is supported by studies showing that this test is a good tool to use for predicting progression to AD for patients with prodromal AD (Mura et al. 2014; Lemos et al. 2015). In addition, data generated from Roche datasets showed that a cueing index of $\leq$0.67 is a good predictor of cognitive decline. Therefore, the FCSRT cueing index of $\leq$0.67 and a free recall score of $\leq$27 have been selected as inclusion criteria for this study. The cueing index measures the ability of a patient to benefit from being reminded using specific cue words to recall the target word. To prevent patients who have a high free recall and who do not appear to benefit from being reminded from being included simply because of apparent low cueing index, a free recall score of $\leq$27 will also be required. The FCSRT index is consistent with that published by Sarazin et al. (2007) and Auriacombe et al. (2010).

3.3.2 Rationale for Use of a Placebo Control Group

Study WN39658 is a placebo-controlled trial in which patients will be eligible for study participation whether or not patients are receiving standard-of-care medications for AD (i.e., *acetylcholinesterase inhibitors,* memantine, and/or medical *food supplements*). Given that there are currently no approved disease-modifying compounds that could serve as an active control, patients will be randomized to receive gantenerumab or placebo on top of background therapies.

3.3.3 Rationale for Gantenerumab Dosage and Titration Schedule

In the OLE studies, different titration schedules (based on prior double-blind treatment exposure and *APOE* ε4 status) have been utilized to enable all patients to reach a target dose of 1200 mg SC Q4W *while managing the risk for ARIA with MRI monitoring and dose intervention algorithms. In addition, d*ata from the OLE studies support treatment at a low starting dose with a gradual increase in dosing (i.e., slow titration schedule) to reach target dose and to reduce the risk of ARIA findings.

As presented in Section 1.3.2, *a target dose of 510 mg Q2W along with a titration schedule with a low starting dose and gradual increase in dosing (i.e., slow titration schedule) that is expected to reduce the risk of ARIA-E for both APOE carriers and non-carriers have been identified for the current study.*

Therefore, all patients in Study WN39658 (regardless of APOE ε4 status) will receive 120 mg of SC gantenerumab Q4W for 3 months, 255 mg SC Q4W for 3 months, and 510 mg SC Q4W for 3 months prior to reaching target dose of 510 mg Q2W after 9 months of titration (see Section 1.3.2 for additional details about the conversion of G3 dosing regimen to G4 dosing regimen). Based on the model predictions (see Appendix 5), the overall ARIA-E rate is expected to be approximately 26%. An MRI scan, confirming the absence of ARIA-E findings, will be required prior to each dose increase.

3.3.4 Rationale for Treatment Duration

According to the EMA's draft guidance on medicinal products for the treatment of AD and other dementias (EMA 2016), controlled clinical trials aimed at demonstrating short-term improvement in mild to moderate AD should last at least 6 months. In order to establish an effect on disease progression, a distinction between symptomatic and disease-modifying effects of a medicinal product has to be made. In addition to demonstrating a relationship between clinical outcomes and an effect on biomarkers of disease pathology, clinical improvement must be shown over a time period that is relevant to the proposed mechanism of action and the expected natural progression rate of the disease. In AD research, long-term placebo-controlled trials are needed in order to allow time for an efficacious therapy to reverse a longstanding disease process as well as to allow time for a sufficient number of placebo-treated patients to progress. Eighteen months was assumed to be of sufficient length in some recently completed Phase III studies of anti-Aβ antibodies (EMA 2016). In prodromal disease stages, even longer studies may be necessary. In addition, placebo decline is expected to be greater at 24 months relative to 18 months; this greater decline allows *an increased* potential to demonstrate a treatment effect.

A 2-year treatment duration has been selected as the most appropriate duration for assessment of the primary endpoint. The duration is based on the mechanism of action of gantenerumab, which is expected to delay and reduce AD progression over time compared with control. *As 9-month titration period to reach the target dose is needed, a 2-year treatment period may also be appropriate for the assessment of the primary endpoint.* To capture an earlier signal of efficacy, should it be present, assessments relevant to the study objectives will also be obtained at 6, 12, and 18 months.

3.3.5 Rationale for Long-Term Follow-Up

The primary objective of the long-term follow-up is to estimate the long-term safety of gantenerumab over an extended period of time. Study assessments performed 14 and 50 weeks after the last dose of study drug will be used to evaluate the effects of treatment on both efficacy and safety parameters over an extended period after study drug discontinuation. Assessments will be conducted for all patients who discontinue treatment during the study or who complete the study but do not enter the OLE study. Assessments will also allow for the exploration of the long-term effects with declining drug exposure.

3.3.5.1 Rationale for Duration of Study Follow-Up (14 Weeks)

The primary purpose of the 14-week follow-up visit (i.e., 14 weeks after the last dose) is to evaluate the long-term safety of gantenerumab. The apparent terminal half-life of gantenerumab is in the order of 24 days, and gantenerumab is cleared from plasma after approximately 16 weeks (approximately 5 half-lives). Therefore, safety assessments performed 14 weeks after the last dose are considered sufficient to evaluate residual effects on peripheral safety outcomes. In addition, efficacy assessments at the follow-up visit may support an enduring effect of gantenerumab after treatment is stopped.

3.3.5.2 Rationale for Long-Term Follow-Up (50 Weeks)

Assessments performed 50 weeks after the last dose will be used to evaluate the long-term effects of study drug on both efficacy and safety parameters. The assessments will allow for the exploration of the long-term effects of study drug given the expected level of decline over this period. Patients will not be restricted from starting new treatment and therefore, the analysis will be considered exploratory.

3.3.6 Rationale for Primary Outcome Measure: Clinical Dementia Rating–Sum of Boxes

AD is considered a continuous disease that passes through consecutive stages without discrete transition points. Thus, the use of a single endpoint across both subpopulations of *early* (prodromal to mild) AD is consistent with the current understanding of AD.

Showing the benefit of new therapies for patients in the early stages of AD is challenging, owing to the lack of sensitive assessment tools. Use of the CDR-SOB as the primary outcome measure for studies of *early* (prodromal to mild) AD enables simultaneous demonstration of benefit on primary symptoms and clinical relevance (Aisen 2009, 2011), while also ensuring use of a clinical outcome assessment with adequate measurement properties (FDA 2013).

The Washington University CDR is a global assessment instrument that yields global scores (GS) and SOB scores. The CDR is derived from a semi-structured interview with the patient and an appropriate informant, and it rates impairment in six categories (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) on a 5-point scale for which 0 = no impairment,

0.5=questionable impairment, and 1, 2, and 3=mild, moderate, and severe impairment, respectively. From the six individual category ratings, or box scores, the CDR-GS is established by clinical scoring rules, for which CDR 0=no dementia and CDR 0.5, 1, 2, or 3=questionable, mild, moderate, or severe dementia, respectively (Morris 1993). The CDR-SOB score is a detailed quantitative general index that provides more information than the CDR-GS in patients with *early* (prodromal to mild) dementia (Coley et al. 2011; Cedarbaum et al. 2013). In particular, the CDR-SOB has been proposed for use in longitudinal assessment of dementia and is widely used in AD studies as a global measure of disease progression (Williams et al. 2013). The FDA's draft guidance for developing drugs for the early stages of disease suggests that a composite scale, validated in patients with early-stage disease that includes both cognition and function as a single primary efficacy outcome measure, is appropriate. The CDR-SOB is an example of a measure that fulfills these criteria (FDA 2013) and is now being utilized as the sole primary endpoint in several studies utilizing patient populations with *early* (prodromal to mild) AD, including the CREAD (crenezumab) and PRIME (aducanumab) studies.

3.3.7 Rationale for Pharmacokinetic Sampling

A sparse sampling schedule is being utilized to minimize patient burden and yet provide an adequate characterization of the population PK profile of gantenerumab. The PK data may be combined with available data from other gantenerumab studies and may be used to assess exposure–response relationships for relevant imaging, CSF, plasma PD biomarkers, ECGs, and efficacy and safety outcomes in patients with *early* (prodromal to mild) AD, as appropriate.

3.3.8 Rationale for Biomarker Assessments

The following biomarker assessments described in Sections 3.3.8.1 (CSF), 3.3.8.2 (PET imaging), and 3.3.8.3 (brain volumetry, connectivity, and fiber tract integrity) will be used to investigate the effect of gantenerumab on the underlying pathology of AD in the patient population.

3.3.8.1 Cerebral Spinal Fluid Biomarkers

Amyloid plaque deposition, neurofibrillary tangle formation, and neuronal degeneration are known pathologic features of AD. Decreased CSF $A\beta_{1-42}$ and elevated CSF t-tau and p-tau are considered a biochemical signature of AD. Accumulating evidence suggests that low CSF $A\beta_{1-42}$ reflects underlying amyloid plaque pathology, whereas increased t-tau and p-tau levels may be reflective of neurodegeneration and/or tau pathology. Amyloid deposition may be the initiating event in the cascade of pathologic processes underlying AD, whereas tau pathology appears to be a subsequent event, and more associated with neurodegeneration. Therefore, t-tau and p-tau may be studied as downstream biomarkers of the primary target of anti-amyloid therapies such as gantenerumab.

Although biomarkers indicative of certain neuropathologies are not surrogate markers for efficacy, there is some evidence that anti-Aβ treatments may cause changes in these biomarkers. A neuropathologic study of patients with AD from Study AN1792 suggests that active amyloid immunotherapy ameliorates neurite abnormalities and tau pathology through decreased tau phosphorylation (Serrano-Pozo et al. 2010). In a pooled analysis of CSF data from two Phase II trials with bapineuzumab in patients with mild to moderate AD, a decrease in both p-tau and t-tau levels relative to baseline was observed in the bapineuzumab group after 12 months of therapy (Blennow et al. 2010). These findings were confirmed in two Phase III studies with bapineuzumab (Sperling et al. 2012) as well as in Study WN25203 with gantenerumab. In Study WN23203, CSF biomarkers were analyzed for changes in multiple proteins, including $A\beta_{1-42}$, t-tau, p-tau, and neurogranin, over the 2-year period. Markers of neurodegeneration were significantly reduced in the 225-mg gantenerumab group compared with placebo over 2 years, with greater relative reduction in p-tau relative to t-tau. The greatest effect was reduction in p-tau in the 225-mg gantenerumab arm at 2 years relative to the change in the placebo arm. There was no treatment effect on CSF $A\beta_{1-42}$ (Nikolcheva et al. 2015). Because no evidence of efficacy was demonstrated with these therapies in clinical trials *yet,* changes in these biomarkers *provide meaningful information about the pharmacodynamic effects of gantenerumab and the effect on* pathologic processes underlying AD.

Based on these data and on the proposed mechanism of action of gantenerumab, levels of CSF t-tau and p-tau *and additional exploratory biomarkers reflecting neurodegeneration* will be assessed at baseline and following treatment. Because gantenerumab is expected to clear amyloid from the brain, levels of CSF $A\beta_{1-42}$ will also be measured.

3.3.8.2 Positron Emission Tomography

The definitive diagnosis of AD requires the presence of progressive dementia during life and the postmortem presence of neuropathological lesions (i.e., neuritic plaques composed of β-amyloid aggregates and neurofibrillary tangles formed from hyperphosphorylated tau protein). However, imaging approaches using ligands that demonstrate high affinity for aggregated amyloid are able to provide an assessment of deposition in vivo, which can be evaluated over time (Clark et al. 2011).

3.3.8.3 Brain Volumetry, Connectivity, and Fiber Tract Integrity

A characteristic feature of AD is neuronal destruction. Such neuronal loss is demonstrated at a macroscopic level by progressive cerebral atrophy, which can be tracked on MRI (Fox and Kennedy 2009). Multiple changes in brain anatomy beyond those associated with normal aging have been reported in patients with AD (e.g., enlarged ventricles, decreased cortical thickness, decreased total brain volume, and hippocampal atrophy), and there is evidence for strong correlations between these imaging biomarkers and functional cognitive measures (Li and Wahlund 2011). Based on volumetric MRI measurements, the two most established markers of disease

progression in longitudinal observational studies are hippocampal and whole brain atrophy (Fox et al. 2000, 2005; Jack et al. 2010), with ventricular expansion a related quantitative marker.

Therefore, to quantify the effects of gantenerumab on neurodegeneration, whole brain volume, ventricular enlargement, and regional brain volume changes will be assessed at screening and following treatment. All MRI reads and volume measures will be conducted by the central reader.

In addition to the structural brain volume changes, changes in brain functioning of patients will be assessed using a blood oxygenation level-dependent (BOLD) resting-state functional MRI (rs-fMRI) procedure (at sites where this procedure is available) with a paradigm-free procedure (Grecius et al. 2004; Filippi and Agosta 2011). Increased concentrations of Aβ in the brains of patients with AD contribute to neuronal degeneration in the brain over time and have been associated with reduced functional connectivity of various brain networks using rs-fMRI (Sheline et al. 2010; Binnewijzend et al. 2012; Brier et al. 2012; Sheline and Raichle 2013). Resting-state functional connectivity has been found to be decreased in brain regions such as the hippocampus, the default mode network (regions such as precuneus, anterior cingulate, and parietal and temporal cortices), and cortical regions in which the functional connectivity is continuously decreased as disease progresses. It has also been found to be decreased in cognitively normal elderly patients with brain amyloid deposition (PiB+PET scans). Alteration of the decreased brain functional connectivity has been shown using therapeutic interventions such as memantine (Lorenzi et al. 2011) or donepezil in patients with AD (Goveas et al. 2011; Solé-Padullés et al. 2013). Increased brain functional connectivity was found already after 3 months of treatment with donepezil, which correlated with changes in cognitive measures such as the ADAS-Cog (Goveas et al. 2011; Solé-Padullés et al. 2013). Therefore, therapeutic interventions, which act to remove Aβ from the brains of patients with AD, may help to reverse the altered functional connectivity presumably caused by the accumulation of Aβ in the brain.

The integrity of white matter tracts will be assessed prior to and after treatment with gantenerumab using diffuse tensor imaging (DTI)-MRI techniques. DTI-MRI is based on the measurement of diffusion properties of water molecules in the axonal fiber tracts in white matter. Whereas water molecules can diffuse isotropically in CSF, they are restricted axially in white matter bundles. Widespread group differences in the degree of anisotropic diffusion, or fractional anisotropy (FA), has been seen between patients with AD and healthy subjects (Jack et al. 2015). Greater FA values are thought to indicate greater white matter integrity. Likewise, mean diffusivity, which measures the average rate of diffusion in all directions, has been shown to be higher in AD groups compared with healthy controls, presumably owing to increased white matter injury in patients with AD (Nir et al. 2013).

At sites having the required software and hardware, rs-fMRI (BOLD rs-fMRI) and DTI-MRI will be performed when feasible during the same scanning session as the structural MRI to assess functional brain connectivity and fiber tract integrity before and after treatment with gantenerumab.

4. MATERIALS AND METHODS

4.1 PATIENTS

This study will enroll approximately *760* patients with increased brain amyloid burden (defined according to CSF or PET criteria), objective memory impairment indicated by cognitive assessment, and a diagnosis of probable AD or prodromal AD based on relevant NIA/AA criteria during the global enrollment phase. Additional criteria are defined in Sections 4.1.1 and 4.1.2.

An increase in sample size may be considered in the event of changes to the sample size assumptions on the basis of blinded data review or factors external to the study.

If at least 1 patient is enrolled *at sites* in *mainland* China*, Hong Kong, and Taiwan that are recognized by the CFDA* during the global enrollment phase, additional patients may be enrolled in a China extension to ensure a *total enrollment that is* sufficient *to support* registration in China. All patients enrolled *at CFDA-recognized sites* in the global enrollment phase will be included in the primary analysis.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Ability to provide written consent signed by the patient (co-signed by the patient's legally authorized representative, if required by the local regulations, guidelines, and independent Ethics Committee [EC] or Institutional Review Board [IRB])
- Age 50–90 years old at screening, inclusive
- Availability of a person (referred to as the "study partner" throughout this protocol) who:
  - *Agrees to participate throughout the 2 years duration of study*
  - *In the investigator's judgment,* has frequent and sufficient contact (e.g., 5 times per week or approximately 10 hours per week) with the patient
  - *In the investigator's judgment, is* able to provide accurate information regarding the patient's cognitive and functional abilities, *including knowledge about domestic activities, hobbies, routines, social skills, and basic activities of daily life; work and educational history; cognitive performance including memory abilities, language abilities, temporal and spatial orientation, judgment and problem solving; emotional and psychological state; and can report any changes in the general health status*
  - Agrees to provide information *and to complete all aspects of the study* at clinic visits (which require partner input for scale completion)

  - Signs the necessary Informed Consent Form(s), and has sufficient cognitive capacity to accurately report on the patient's behavior *as well as* cognitive and functional abilities
  - Is *fluent* in *the language used at the site and has* sufficiently good general health to have a high likelihood of maintaining the same level of interaction with the patient and participation in study procedures throughout the duration of the study

    Every effort should be made to have same study partner participate throughout the duration of the study.
- Fluency in the language of the tests used at the study site
- Willingness and ability to complete all aspects of the study (including MRI, lumbar puncture [if applicable], clinical genotyping, and PET imaging [if applicable])

  The patient should be capable of completing assessments either alone or with the help of the study partner.
- Adequate visual and auditory acuity, in the investigator's judgment, sufficient to perform the neuropsychological testing (eye glasses and hearing aids are permitted)
- Evidence of AD pathological process, as confirmed by CSF tau/$A\beta_{42}$ or on amyloid PET scan by qualitative read by the core/central PET laboratory
- Demonstrated abnormal memory function at screening (FCSRT cueing index ≤ 0.67 and free recall ≤ 27)
- Screening MMSE score ≥ 22 and CDR-GS of 0.5 or 1.0
- Probable AD dementia (consistent with NIA/AA core clinical criteria for probable AD dementia) (McKhann et al. 2011) or prodromal AD (consistent with the NIA/AA diagnostic criteria and guidelines for mild cognitive decline due to AD) (Albert et al. 2011)
- If the patient is receiving symptomatic AD medications, a stable dosing regimen for at least 3 months prior to baseline and until randomization
- Agreement not to donate blood or blood products for transfusion for the duration of the study and for 1 year after final dose of study drug
- Agreement not to participate in other research studies for the duration of this trial and its associated substudies
- For enrollment in the China extension, *patients must have residence in mainland China, Hong Kong, or Taiwan and be of Chinese ancestry.*
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least *16* weeks after the last dose of study drug

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

4.1.2.1 Exclusions Related to Central Nervous System Disorders

Patients who meet any of the following criteria related to CNS disorders will be excluded from study entry:

- Any evidence of a condition other than AD that may affect cognition, including, but not limited to, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, *Parkinson* disease, corticobasal *syndrome*, Creutzfeldt-Jakob disease, progressive supranuclear palsy, frontotemporal *lobar* degeneration, Huntington disease, normal pressure hydrocephalus, seizure disorder, delirium or hypoxia
- History or presence of clinically evident *systemic* vascular disease (e.g., clinically significant carotid/vertebral *artery* stenosis or plaque, aortic aneurysm*),* that in the opinion of the investigator has the potential to affect cognitive function
- *History or presence of clinically evident cerebrovascular disease (e.g., intracranial or cerebral vascular malformations, aneurysm, intracranial macrohemorrhage)*

  Patients with asymptomatic developmental venous anomalies may be eligible after discussion with and approval by the Medical Monitor.
- *History or presence of posterior reversible encephalopathy syndrome*
- History or presence of any stroke with clinical symptoms within the past 12 months, or documented history within the last 6 months of an acute event that is consistent, in the opinion of the investigator, with a transient ischemic attack
- History of severe, clinically significant (persistent neurologic deficit or structural brain damage) CNS trauma (e.g., cerebral contusion)
- History or presence of intracranial mass (e.g., glioma, meningioma) that could potentially impair cognition
- Presence of infections that affect brain function or history of infections that resulted in neurologic sequelae (e.g., HIV, syphilis, neuroborreliosis, and viral or bacterial meningitis and encephalitis)
- History or presence of systemic autoimmune disorders that potentially cause progressive neurologic disease with associated cognitive deficits (e.g., multiple sclerosis, lupus erythematosus, anti–phospholipid antibody syndrome, and Behçet disease)

- History of schizophrenia, schizoaffective disorder, major depression, or bipolar disorder

  History of major depression is acceptable if patient has had no episode within the past year or is considered in remission or depression is controlled by treatment.
- At risk *for* suicide in the opinion of the investigator
- Alcohol and/or substance abuse or dependence (according to the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, Version 5) within the past 2 years

  Nicotine use is allowed.

  Marijuana use is not allowed and must be discontinued at least 3 months before screening.

4.1.2.2 Imaging-Related Criteria

Patients who meet any of the following imaging criteria will be excluded from study entry:

- According to the MRI central reader, MRI evidence of any of the following:
  - >2 lacunar infarcts
  - Any territorial infarct >1 cm^3
  - Any white matter lesion that corresponds to an overall Fazekas score of 3 that requires at least one confluent hyperintense lesion on the fluid-attenuated inversion recovery (FLAIR) sequence, which is ≥ 20 mm in any dimension
- Combined number of microbleeds and areas of leptomeningeal hemosiderosis (i.e., cumulative ARIA-H) on MRI more than five (and should not include any disseminated leptomeningeal hemosiderosis) based on the review performed by the central reader prior to randomization
- Presence of any other significant cerebral abnormalities, including ARIA-E, as assessed on MRI
- Inability to tolerate MRI procedures or contraindication to MRI, including, but not limited to, presence of pacemakers not compatible with MRI, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan, or any other clinical history or examination finding that, in the judgment of the investigator, would pose a potential hazard in combination with MRI

4.1.2.3 Cardiovascular Disorders

Patients who meet any of the following criteria related to cardiovascular disorders will be excluded from study entry:

- History or presence of clinically symptomatic atrial fibrillation requiring maintenance therapy

  Patients who experienced non-valvular atrial fibrillation that resolved more than 1 year ago and was not associated with prior stroke are eligible.

- Within the last year, unstable or clinically significant cardiovascular disease (e.g., myocardial infarction)

  Heart failure classified as New York Heart Association Class *I* or *II* cardiac disease *is allowed if not associated with hospitalization within the previous 12 months.*

- Uncontrolled hypertension (e.g., blood pressure generally $>$160 mmHg systolic or $>$95 mmHg diastolic)

4.1.2.4 Hepatic and Renal Disorders

Patients who meet any of the following criteria related to hepatic and renal disorders will be excluded from study entry:

- Chronic kidney disease, indicated by creatinine clearance $<$30 mL/min to be calculated by the central laboratory using the Cockcroft-Gault formula at screening, which remains $<$30 mL/min if retested
- Confirmed and unexplained impaired hepatic function as indicated by screening AST or ALT $\geq 3\times$ the upper limit of normal (ULN) or total bilirubin $\geq 2\times$ ULN

4.1.2.5 Infections and Immune Disorders

Patients who meet any of the following criteria related to infections and immune disorders will be excluded from study entry:

- History of, or known to currently have HIV infection, or hepatitis B or hepatitis C infection that has not been adequately treated in the opinion of the investigator, or history of spirochete infection of the CNS (e.g., syphilis, Lyme disease, or borreliosis)
- Systemically, clinically significantly immunocompromised patients, owing to continuing effects of immune-suppressing medication

4.1.2.6 Metabolic and Endocrine Disorders

Patients who meet any of the following criteria related to metabolic and endocrine disorders will be excluded from study entry:

- Abnormal thyroid function as indicated by abnormal screening tests that are judged to be clinically significant by the investigator, or abnormal thyroid function that requires a new treatment or an adjustment of current treatment

  A patient may be rescreened if there is no improvement in cognition in the investigator's judgment after 3 months of adequate treatment for thyroid function.

- *Patients with evidence of folic acid deficiency (as indicated by folic acid level below the lower limit of normal) or vitamin B-12 deficiency (as indicated by vitamin B-12 level below the lower limit of normal and/or methylmalonic acid levels above ULN)*

  A patient may be rescreened if there is no improvement in cognition after 3 months of adequate treatment for folic acid or vitamin B-12 deficiency.

- Screening hemoglobin A_{1c} (HbA_{1C}) > 8% (retesting is permitted if slightly elevated) or poorly controlled insulin-dependent diabetes (including hypoglycemic episodes)

  A patient may be rescreened after 3 months to allow optimization of diabetic control.

4.1.2.7 Exclusions Related to Medications

The following medications are prohibited for a pre-specified duration prior to study start, as indicated, and during the entire period of study participation (Patients who start these medications during the study may be withdrawn from study treatment*; for additional details on prohibited medications, please refer to Appendix 7*):

- Any previous administration of gantenerumab or active immunotherapy (vaccine) that is being evaluated to prevent or postpone cognitive decline
- Any passive immunotherapy (immunoglobulin) or other long–acting biologic agent that is under evaluation to prevent or postpone cognitive decline within 1 year of screening
- Any other investigational treatment or any other treatment with a monoclonal antibody within 5 half-lives or 4 months prior to screening, whichever is longer
- Any previous treatment with medications specifically intended to treat Parkinson symptoms or any other neurodegenerative disorder within 1 year of screening and with no *plans to initiate such medications* prior to randomization

  Certain medications are acceptable if the patient is taking the medicine for a non-neurodegenerative disorder, such as restless leg disorder (e.g., pramipexole).
- Typical antipsychotic or neuroleptic medication within 6 months of screening and with no planned changes prior to randomization except as brief treatment for a non-psychiatric indication (e.g., emesis)

  Atypical antipsychotic medications are not allowed except for intermittent short-term use and will need to be discontinued 2 days or *at least* 5 half-lives (whichever is longer) prior to any neurocognitive assessment.
- Anti-coagulation medications within 3 months of screening with no *plans to initiate any* prior *to* randomization

  Anti-platelet treatments (e.g., aspirin, clopidogrel, and dipyridamol) are permitted.

  Short-term, perioperative use of anticoagulant medications will not result in permanent discontinuation from the study; however, any such use must be discussed prospectively with the Medical Monitor and may require temporary study drug interruption.
- Chronic use of opiates or opioids (including long-acting opioid medication) within 3 months of screening with no *plans to initiate any* prior *to* randomization

  Intermittent short-term use of short–acting opioid medications for pain is permitted except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

- Stimulant medications (amphetamine, methylphenidate preparations, or modafinil) within 1 month of screening and throughout the study
- Chronic use of benzodiazepines, barbiturates, or hypnotics from 3 months before screening and with no *plans to initiate any* prior *to* randomization

  Intermittent short-term use of benzodiazepines, buspirone, or short-acting hypnotic medication for sleep or anxiety is allowed except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

4.1.2.8 Other Exclusions

Patients who meet any of the following criteria will be excluded from study entry:

- Other causes of intellectual disability that may account for cognitive deficits observed at screening (e.g., static encephalopathy, closed brain injury, mental retardation)

  This may be based on, for example, patient's sufficient education or work experience.
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study
- Deformity of the lumbosacral region of the spine that in the opinion of the investigator would contraindicate lumbar puncture in patients who will have lumbar puncture
- Clinically significant abnormal screening blood, CSF (if applicable), or urine results that remain abnormal at retest
- Impaired coagulation (screening prothrombin time [PT] $> 1.2\times$ the ULN that remains abnormal on retest)
- History of cancer, with the following exceptions:
  - If considered to be cured
  - If not being actively treated with anti-cancer therapy or radiotherapy and, in the opinion of the investigator, is not likely to require treatment in the ensuing 5 years
  - For prostate cancer or basal cell carcinoma, no significant progression over the previous 2 years
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins, including gantenerumab
- Hypersensitivity to any of gantenerumab excipients
- Any other severe or unstable medical condition that, in the opinion of the investigator or Sponsor, could be expected to progress, recur, or change to such an extent that it could put the patient at special risk, bias the assessment of the clinical or mental status of the patient to a significant degree, interfere with the patient's ability to complete the study assessments, or would require the equivalent of institutional or hospital care

- Residence in a skilled nursing facility such as a convalescent home or long-term care facility: Patients who subsequently require residence in such facilities during the study may continue in the study and be followed for efficacy and safety, provided that they have a study partner who meets the minimum requirement

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Randomization will be performed centrally using an interactive voice or Web-based response system (IxRS). After screening, patients who meet all eligibility criteria will be randomly assigned to one of two treatment groups (gantenerumab or placebo). The ratio will be 1:1, one active to one placebo. The randomization method will be stratified block-randomization. Randomization to treatment allocation will be stratified by geographic region *(Western Europe vs. Rest of the World vs. North America)*, patient *APOE* ε4 status (carrier vs. non-carrier), patient stage of disease (prodromal vs. mild AD), use of AD medication (present vs. absent), and participation in the longitudinal amyloid *and tau* PET *substudies*. Except in circumstances in which a health authority, EC, or IRB requires it, a patient will not be told of his or her *APOE* ε4 status. Individual patient *APOE* ε4 genotype results will be blinded to patients, investigators, and the Sponsor. *APOE* ε4 status information will be supplied directly to the IxRS vendor by the central testing laboratory so that the information can be incorporated at the time of randomization. For patients for whom *APOE* ε4 status is already known, the results will be blinded to the Sponsor and as much as possible to the site and central MRI reader.

The study is to be conducted in a double-blind manner to minimize potential bias from investigators and patients. The Sponsor will be blinded to study treatment. The Master Randomization or Master Medication List will not be available at the study center, to Roche monitors, Roche project statisticians, or to the project team at Roche. Unblinding should not occur except in the case of emergency situations where knowledge of the study drug assigned would affect patient *care*. The investigator should make every effort to contact Roche before unblinding a patient. In the event that the investigator unblinds a patient without prior notification, the investigator must contact Roche within 1 working day of the event. Any request from the investigator for information about the treatment administered to study patients for another purpose must be discussed with the Medical Monitor.

If unblinding is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the investigator wants to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event).

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.2.2) that are considered by the investigator or Sponsor to be related to study drug.

4.3 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is gantenerumab.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Gantenerumab and Placebo

Gantenerumab and placebo will be supplied by the Sponsor as *liquid formulation* ready for SC administration. Packaging of the study drug will be overseen by the Roche Clinical Trial Supplies Department and will bear a label with the identification required by local law, the protocol number, study drug identification, and dose. The packaging and labeling will be in accordance with Roche standard and local regulations. Upon receipt of the investigational products at the site, site personnel should check the product for damage and verify the proper identity, quantity, and integrity of the study drug. Site personnel should report any deviations or product complaints to the monitor upon discovery. For further details, please refer to the Gantenerumab Investigator's Brochure.

For information on the formulation and handling of gantenerumab, see the pharmacy manual and Gantenerumab Investigator's Brochure.

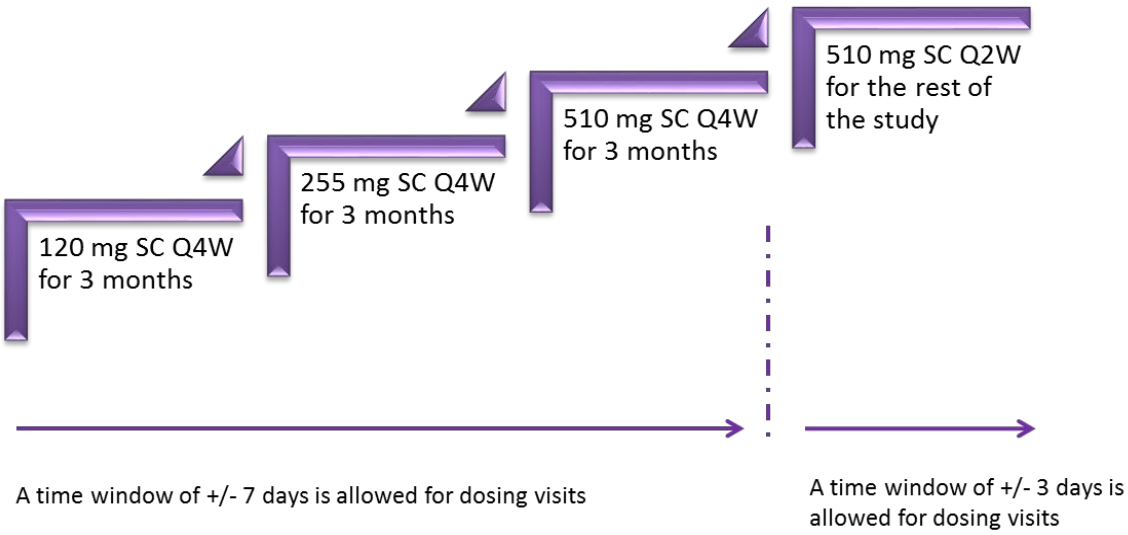
4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Gantenerumab and Placebo

Gantenerumab or placebo will be administered by SC injection to all patients.

Gantenerumab will be administered by SC injection to all patients randomized to the active treatment arm, regardless of *APOE* ε4 status, at a dose of *120* mg SC Q4W for 3 months, *255* mg SC Q4W for 3 months, and *510* mg SC Q4W for 3 months, prior to reaching *the target dose* (see Figure 6). Once the target dose is reached, study drug will be administered *every 2 weeks (Q2W administration of 510 mg SC gantenerumab)*. The switch to a Q2W administration schedule allows decreasing the number of SC administrations in the abdomen per visit.

Figure 6 Overall Gantenerumab Dosing Design



Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous.

For Q4W injections, a time window of ±7 days is allowed for dosing visits. Once study drug is administered Q2W, the time window for dosing visits is ±3 days.

Regardless of dose, each patient will undergo up to a total of 43 dosing visits in the study. Injections will be administered as one 0.8-mL (120-mg dose), one 1.7-mL (255-mg dose), or two 1.7-mL injections (510-mg dose) subcutaneously to the abdomen, respectively.

Placebo of identical composition (except protein) and identical volume to gantenerumab will be administered by SC injection to all patients randomized to placebo at the same frequency and using the same route of administration.

On study drug administration days that include efficacy assessments (see the schedule of activities in Appendix 1), study drug must be administered at the clinical site. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

At applicable sites, study drug may be administered by a trained nursing professional at the patient's home or another suitable location, if the patient has given written informed consent to participate in home nursing visits.

Rules for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.3.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.2.2 *PET Tracers*

All patients who are enrolled in PET substudies will be assessed by PET imaging using an appropriate PET ligand. For screening, the possible amyloid PET ligands will be florbetapir, florbetaben, and flutemetamol. *According to E.U. guidance, the PET tracers used in the context of this study have been designated as non-IMP. In some regions, according to local regulations, these PET tracers may be considered to be IMP.*

In countries where the PET radioligands are approved for marketing, the approved local product information will be provided, and in countries where they are not approved for marketing, the Investigator's Brochures will be provided.

Details about the PET substudies are described in separate protocols.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (gantenerumab or placebo) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to Gantenerumab

The Sponsor will offer continued access to Sponsor study drug (gantenerumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Sponsor study drug (gantenerumab) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Sponsor study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient

- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Sponsor study drug (gantenerumab) after completing the study if any of the following conditions are met:

- The Sponsor study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the drug or data suggest that the drug is not effective for AD
- The Sponsor has reasonable safety concerns regarding the drug as treatment for AD
- Provision of the drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

All eligible patients will be offered to receive gantenerumab as part of an extension study, as described in Section 3.1.

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 3 months prior to screening to the study completion or discontinuation visit. All such medications (including name, dose, administration schedule, start and end dates) should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients are eligible for study participation whether or not they are receiving approved medication for AD (i.e., *acetylcholinesterase inhibitors,* memantine, *and/*or medical food supplement*s*, where approved). Information about background AD medication (e.g., drug name, dose, and start and stop dates, reason for interruption or modification) has to be captured on eCRF. Randomization will be stratified for patients taking and not taking approved anti-dementia medications.

Adding a new medication or changing the dose of a medication after randomization should occur only for the treatment of an adverse event or in case of AD progression. Whenever possible, a medication listed below should be used if appropriate.

The following medications are permitted if the dose and dose regimen have been stable for at least 3 months prior to screening and are expected to remain stable after screening or if required for treatment of an adverse event after randomization:

- Anticonvulsant medications for an approved pain indication
- Selective serotonin reuptake inhibitors for the treatment of depressive symptoms
- Over-the-counter and/or herbal medications, food additive, or any other agent or supplement intended to improve cognition or reduce cognitive decline
- Medications used to treat a mood or anxiety disorder given as maintenance treatment *(with the exception of benzodiazepine)*
- Intermittent use of short-acting (non-extended release) opioid medications for pain except within 2 days or 5 half-lives (whichever is the longer) of any cognitive assessment (up to a maximum of 3 consecutive days per month)
- Intermittent use of benzodiazepines, including alprazolam, lorazepam, oxazepam, triazolam, or temazepam, or a one-time dose of diazepam or a short–acting hypnotic medication (e.g., zolpidem) if use is intermittent for sleep or anxiety, except *within* 2 days or 5 half-lives (whichever is the longer) prior to any cognitive assessment
- A dose of benzodiazepine for pre-surgical and pre-imaging sedation at appropriate visits if allowed by the EC or IRB
- Intermittent use of centrally acting antihistamine medications except *within* 2 days or 5 half-lives (whichever is the longer) prior to any cognitive assessment
- Under certain circumstances, initiation of anti-hemostasis medications during the study conduct

  Anticoagulation therapy lasting no longer than 3 weeks (e.g., temporary usage during surgery) is permitted. Nevertheless, no anticoagulation therapy should be initiated without discussion with and approval by the Medical Monitor.

Concomitant and excluded therapies for determination of patient eligibility are described in Section 4.1.2.7.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

4.4.2 Prohibited Therapy

Any medication that is prohibited before screening is also prohibited during conduct of the study (see Section 4.1.2.7). If a patient receives any prohibited treatment during the study, the patient may be withdrawn from study treatment.

4.5 STUDY ASSESSMENTS

Refer to Appendix 1 for the schedule of activities to be performed during the study.

At applicable sites, certain study assessments may be performed by a home nursing (HN) professional at the patient's home or nursing center to improve access and convenience for patients participating in the study. The Sponsor will select a healthcare company that will be responsible for providing HN services for participating sites (the HN vendor). The HN vendor is responsible for ensuring that all HN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that HN services are appropriate for a patient and the patient gives written informed consent to participate in HN visits, the HN network will communicate with the patient and the patient's site. HN visits will be scheduled on specified visit days to allow relevant assessments to be performed by the HN professional. The schedule of activities (see Appendix 1) specifies which assessments may be performed by an HN professional.

4.5.1 Informed Consent Forms and Screening Log

All patients and study partners must review, sign, and date the most current IRB/EC-approved written informed consent for participation in the study before any study-specific prescreening assessments, screening tests or evaluation are performed. Informed Consent Forms for enrolled patients and their study partners and for those who are not subsequently enrolled will be maintained at the study site.

All prescreening and screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients prescreened and screened and to confirm eligibility or record reasons for screening failure, as applicable. Prescreening is optional and is covered by a dedicated Informed Consent Form.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), smoking history, use of alcohol, and drugs of abuse. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 3 months prior to screening visit will be recorded. Demographic data will include age, sex, and self-reported race/ethnicity. Medical history and demographic data will be collected at the screening visit only.

As this study is being conducted in multiple geographic regions, it is likely that patients of different ethnic origins will be enrolled in the study. Although there is currently no indication that gantenerumab is metabolized or eliminated differently or that the

treatment effect would be different in patients of different ethnic origins, collecting this information is essential to adequately evaluate the results of this study (e.g., possible differences in PK exposure [concentration of the drug in the blood] or treatment effect).

4.5.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

The schedule of activities indicates when complete physical examinations (including neurological systems) are to be recorded (see Appendix 1, Tables 1 and 2).

Limited, symptom-directed physical examinations should be performed per the schedule of activities (or as clinically indicated). Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

In addition, weight will be obtained at screening, at the Week 104 or early termination visit, and at any other visit as deemed necessary by the investigator. *Height will be obtained at screening only.*

4.5.4 Vital Signs

Vital signs will include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the patient is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements.

Pulse rate will be determined by radial pulse and will be recorded as beats per minute. The pulse rate should be counted for a minimum of 20 seconds at each assessment.

Vital sign measurements may be performed by an HN professional.

The schedule of activities indicates when vital signs (blood pressure and pulse rate) are to be recorded (see Appendix 1).

4.5.5 Cognitive, Functional, and Health Economics Assessments

The assessments described in this section will be performed as outlined in the schedule of activities (see Appendix 1) and in the order specified in Section 4.6.

Whenever possible, there should be consistency in the rater and study partner who complete the scales for each patient throughout the duration of the study. Potential raters will receive training and be approved by the rating scale contract research organization (CRO) prior to being allowed to administer any cognitive assessments or rating scales in the study.

Given that the primary outcome measure in this trial involves subjective judgment, the adequacy of patient and study partner interviews and ratings will be monitored by an endpoint reliability program administered by the rating scale vendor; this is considered an essential part of good research methodology. For the primary endpoint as well as for some other scales, audio recordings may be used for quality assurance purposes. Prior studies have clearly demonstrated that the failure to adequately monitor such ratings can substantially increase the risks of failed trials (Becker and Greig 2008; Kobak 2010).

4.5.5.1 Clinical Dementia Rating Scale

The CDR global score (CDR-GS) *characterizes a patient's level of impairment according to the following categories: 0 (normal), 0.5 (very mild dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia).* The SOB score is a detailed quantitative general index that provides more information than the CDR-GS in patients with mild dementia *(Berg 1988; Morris et al. 2001, O'Bryant et al. 2010) and is scored from 0–18 with higher scores indicating greater impairment.* The CDR characterizes six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The necessary information to make each rating is obtained through a semi-structured interview with the patient and a reliable informant or collateral source (e.g., a study partner).

As much as is feasible, the CDR should be administered to an individual patient by the same assessor throughout the study and that assessor should not perform the MMSE, ADAS-Cog, *Verbal Fluency Task, Coding,* FAQ, or Alzheimer's Disease Cooperative Study Group–Activities of Daily Living (ADCS-ADL). However, if in exceptional circumstances only this assessor is available to perform these other scales, then the CDR patient interview must be completed after the study partner interview but before ADAS-Cog, MMSE, *Verbal Fluency Task, Coding, and other scales are completed. Nevertheless, at screening, baseline, and Week 104, the CDR rater cannot perform other scales than the CDR. In addition, the CDR rater should not be involved in safety assessments and especially should not receive information about any ARIA findings.*

4.5.5.2 Alzheimer's Disease Assessment Scale–Cognitive Subscale

The ADAS-Cog is the most frequently used scale to assess cognition in clinical trials for mild to moderate AD dementia (Rozzini et al. 2007; Connor and Sabbagh 2008; Ihl et al. 2012). More specifically, the ADAS-Cog is a patient-based assessment that measures learning and memory, language production, language comprehension, constructional praxis, ideational praxis, and orientation. The modified version will be used; it has 13 items and includes the addition of delayed word recall and a number of cancellation

subtests, as well as use of only one trial for word recognition (Mohs et al. 1997). Equivalent alternate forms of the word recall, word recognition, and number cancellation subtests will be used in successive test administrations.

4.5.5.3 Mini-Mental State Examination

The MMSE is a set of standardized questions used to evaluate possible cognitive impairment and help stage the severity level of this impairment (Folstein et al. 1975). The questions target six areas: orientation, registration, attention, short-term recall, language, and constructional praxis/visuospatial abilities. The MMSE is a patient-based assessment.

4.5.5.4 Free and Cued Selective Reminding Test–Immediate Recall

The FCSRT-Immediate Recall (FCSRT-IR) is a patient-based assessment that measures memory under conditions that control attention and cognitive processing. Impairments in FCSRT-IR performance have been associated with preclinical and early dementia in several longitudinal epidemiological studies (Grober and Buschke 1987; Sarazin et al. 2007). The 16-word version of the test will be used in this study.

4.5.5.5 Verbal Fluency Task

The category verbal fluency (e.g., animals) is a patient-based assessment that measures speed and flexibility of verbal thought. Verbal fluency tests are sensitive tools for detecting dementia (Pasquier et al. 1995; Lezak et al. 2004) and for monitoring decline over time (Clark et al. 2009).

4.5.5.6 *Coding*

The Coding, also called Digit Symbol Substitution Test (or DSST), is a subtest from the Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV; Wechsler 2008). The Coding is a patient-based assessment that measures speed of processing and associative memory. The test is known to be sensitive to disease progression (Lezak et al. 2004). The 120-second version of the test will be used in this study.

4.5.5.7 Functional Activities Questionnaire

The FAQ (Pfeffer et al. 1982) is an informant-based measure of functional abilities. Informants provide performance ratings of the target person on ten complex higher-order activities.

4.5.5.8 Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory

The ADCS-ADL (Galasko et al. 1997) is the scale most widely used to assess functional outcome in patients with AD (Vellas et al. 2008). The ADCS-ADL is a 23-item informant-based questionnaire that covers both basic activities of daily living (ADL) (e.g., eating and toileting) and more complex ADL or instrumental ADL (e.g., using the telephone, managing finances, preparing a meal). *It has a 4-week recall period. Total scores range from 0–78, with higher scores indicating better functioning.*

4.5.5.9 Zarit Caregiver Interview–Alzheimer's Disease

The Zarit Caregiver Interview–Alzheimer's Disease (ZCI-AD) is a modified version of the Zarit Burden Interview, which was originally designed to reflect the stresses experienced by caregivers for people with dementia (Zarit and Zarit 1990). The modified version includes slight modifications in item and title wording (e.g., removal of "your relative" to refer directly to the patient, removal of "burden" from title) and the use of 11-point numerical rating scales. The ZCI-AD scale consists of 30 items and is completed by the study partner without involvement from the site staff. *It has a 4-week recall period.*

If a patient's study partner is replaced during the study, the ZCI-AD will not be completed by his or her new study partner.

4.5.5.10 Quality of Life–Alzheimer's Disease

The Quality of Life–Alzheimer's Disease (QoL-AD) was developed to assess QoL in patients who have dementia (Logsdon et al. 1999, 2002). The QoL-AD consists of 13 items covering aspects of patients' relationships with friends and family, physical condition, mood, concerns about finances, and overall assessment of QoL. *The total score is the sum of the 13 items and ranges from 13–52, with higher scores indicating better HRQOL.*

In this study, the QoL-AD will be administered in a standardized, structured interview format to patients by investigative staff in order to gather patient responses about QoL. The study partner will also complete the study partner version of the questionnaire to enable proxy responses from the study partner.

4.5.5.11 EQ-5D

The EuroQoL–Five Dimensions (EQ-5D) is a standardized measure of health status designed to provide a simple generic measure of health for clinical and economic appraisal. It is broadly applicable across a wide range of health conditions and treatment.

The EQ-5D assesses five domains to provide a health state index. These are anxiety/depression, pain/discomfort, usual activities, mobility, and self-care.

The following two versions will be used in this study:

- EQ-5D-5L Proxy, Version 1: The study partner (the proxy) is asked to rate the patient's health-related QoL in his or her (the proxy's) opinion.
- EQ-5D-5L, Self-Complete Version: The study partner is asked to rate his or her own health-related QoL.

4.5.5.12 Resource Utilization in Dementia Scale

The Resource Utilization in Dementia (RUD) scale (Wimo et al. 2003) aims to document formal and informal resource use in a clinical trial setting. The RUD-Lite captures the most important elements in dementia care: accommodation, informal care,

hospitalizations, and community care services. Information on study partner sociodemographics in addition to working status and effect on productivity will be collected. The amount of informal care will be collected according to three types of care: personal ADL, instrumental ADL, and supervision. Data on accommodation and temporary changes in accommodation during the last month and the duration of these will be collected according to four levels of accommodation: own home, intermediate forms of accommodation, dementia-specific residential accommodation, and nursing home. Resource utilization will be recorded as the number of nights spent in different types of hospital wards, the number of visits to the most common types of outpatient care, and the number of visits in community care services.

4.5.5.13 Neuropsychiatric Inventory Questionnaire

The Neuropsychiatric Inventory–Questionnaire (NPI-Q) (Kaufer et al. 2000) was developed to assess a wide range of behaviors encountered in dementia patients, to provide a means of distinguishing severity of behavioral changes, and to facilitate rapid behavioral assessment through the use of screening questions. It is an informant-based instrument in which 12 behavioral domains are evaluated. *The recall period is the past month, and severity scores range from 0–36, with higher scores indicating greater severity.* The study partner's distress portion of the scale will not be used in this study.

4.5.5.14 Electronic Assessment of Rating Scales

The following rating scales will be captured electronically and transferred to the database directly from the core laboratory: ADAS-Cog, Verbal Fluency Task, ADCS-ADL, CDR, MMSE, FCSRT, FAQ, AD QoL, EQ-5D, RUD-Lite, NPI-Q, and CSSR-S.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

4.5.6.1 Standard Laboratory Samples

Samples for the following laboratory tests will be sent to a central laboratory for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

- Serum chemistry: AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory)

  HbA_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed according to the schedule of activities.

- Hematology: hemoglobin, hematocrit, RBC count (with morphology), WBC count, platelets, basophils, eosinophils, lymphocytes, monocytes, neutrophils, and WBC–other total counts
- Screening serology: HIV, hepatitis B, and hepatitis C
- Coagulation: PT

- Urine for drugs of abuse: At screening only, urine samples will be analyzed for the presence of the following drugs: amphetamine, benzodiazepines, cannabinoids, opiates, cocaine, barbiturates, and methadone. Results will be used to verify patient eligibility pertaining to drugs of abuse. Inconclusive results may be repeated once during the screening period. Investigators should use their best clinical judgment in cases where results may be erroneous (e.g., permitted use of opiates or ingestion of food/food supplements).
- Urinalysis: At screening only, urinalysis will be performed at the site by dipstick for blood, protein, glucose, and pH. Microscopic examination will be performed by the central laboratory if blood and/or protein results are positive or strongly positive.
- Urine for pregnancy test: Urine pregnancy testing will be performed at each dosing visit (prior to dose administration) for women of childbearing potential (including those who have had a tubal ligation), and at the site for any other female participants if required by local regulations. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory.

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

4.5.6.2 Biomarker Sampling

Samples will be obtained from all patients and will be used for research purposes to identify dynamic biomarkers that may be predictive of response to treatment with gantenerumab (in terms of dose, safety, and tolerability) and will help to better understand the pathogenesis, course, and outcome of AD and related diseases.

For patients who consent to the optional Roche Research Biosample Repository (RBR) residual biomarker samples will be kept for future biomarker research (see Section 4.5.12).

The procedures for the collection, handling, and shipping of biomarker samples are specified in the Sample Handling and Logistic Manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.12), biomarker samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Roche may keep information about screening test results, medical history, and demographic information for all patients (including non-eligible patients) for future development of diagnostic tests related to Aβ, *APOE* genotype, and AD, as well as additional analyses.

Cerebrospinal Fluid *and Serum* Sampling (for CSF-Enrolled Patients Only)

CSF samples and matching serum samples will be obtained from patients who choose to provide CSF samples during screening (CSF-enrolled patients) for confirmation of Aβ and tau levels for eligibility purposes (mandatory) and for monitoring Aβ and tau levels, as well as other CSF biomarkers at different timepoints during the study. *The matching serum samples may be used to determine parameters that allow the assessment of the blood-brain barrier status and/or inflammatory processes in the brain, such as CSF/serum albumin ratio, CSF/serum IgG and IgM indices, and oligoclonal bands. CSF and serum* samples will be collected according to the schedule of activities (see Appendix 1).Lumbar puncture will be performed by an individual who meets all local requirements and is proficient in the procedure. Lumbar puncture procedures and post–lumbar puncture care will be performed in accordance with local practice. CSF sampling should be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters. Procedures for the processing of the CSF samples can be found in the Sample Handling and Logistics Manual.

Approximately 12 mL of CSF will be collected at each timepoint. The sample will be divided into aliquots onsite and used for the following:

- Central measurement of gantenerumab levels in the CSF and biomarker analysis, including $A\beta_{1-42}$, t-tau, p-tau, as well as some exploratory markers. Samples may also be used to support the development of biomarker assays for diagnostic use.

Unused CSF samples will be kept for future biomarker research if the patient gives consent to participate in the RBR (see Section 4.5.12.5).

Clinical Genotyping

During screening, three mandatory 3-mL whole blood samples will be obtained for DNA extraction from every patient who has consented to participate in the study. All patients will be evaluated for *APOE* ε4 status, clusterin (apolipoprotein J) genotypes, and Fcγ-receptor genotype. The Fcγ-receptor genotype may play a role in PK and PD variability of antibody-based therapeutic agents and may be predictive of response and non-response.

APOE ε4 status will be determined and will be blinded to the Sponsor, investigator, and patient and will not be shared with the investigator or the patient until the study is unblinded (unless required for patient safety or by the relevant health authority or IRB/EC). Patients will have access to this information if they elect to at the end of the study. If already known, the *APOE* ε4 status will still need to be confirmed and should be kept blinded from the Sponsor. In addition, as much as possible, patient *APOE* ε4 status should remain blinded to the site and central MRI readers.

Samples and data may be used for future research or diagnostic test development.

The procedures for the collection, handling, and shipping of clinical genotyping samples are specified in the Sample Handling and Logistics Manual.

RNA Sampling

During screening and at a subsequent visit as detailed in the schedule of activities (see Appendix 1), two 2.5-mL whole blood samples will be obtained for RNA extraction from every patient who has consented to participate in the study. The sample may be used to evaluate clusterin messenger RNA and other exploratory genetic markers in peripheral blood (see Section 4.5.12).

Plasma Sampling

At *screening* and at subsequent visits as detailed in the schedule of activities (see Appendix 1), one 6-mL whole blood sample will be obtained for plasma extraction from every patient who has consented to participate in the study.

This sample will be used to evaluate exploratory plasma biomarkers in peripheral blood.

4.5.6.3 Anti-Drug Antibody Sampling

Blood samples will be collected to assess the possible development of ADAs in all patients as noted in the schedule of activities (see Appendix 1). Plasma samples will be analyzed for antibodies to gantenerumab using a bridging ELISA.

Samples collected from patients receiving placebo will not be assessed in the first instance but retained for subsequent analysis if appropriate.

Unused sample material may also be used for the purposes of current ADA assay improvement.

The procedures for the collection, handling, and shipping of PK and ADA samples are specified in the Sample Handling and Logistics Manual supplied to the site.

4.5.6.4 Pharmacokinetic Sampling

Plasma Gantenerumab Samples

Blood samples will be collected to evaluate the pharmacokinetics of gantenerumab in plasma as noted in the schedule of activities *(see Appendix 1)*.

An additional PK sample for the assessment of plasma concentrations of gantenerumab will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E, or occurrence of ARIA-H meeting discontinuation criteria.

Samples from patients receiving placebo may not be assessed at once but will be retained for subsequent analysis if appropriate. Samples will not be analyzed in real time but will be batched for analysis throughout the study.

Unused sample material may be used for the purpose of current gantenerumab assay improvement and for the quantification of specific gantenerumab glycan species.

Processing, storage, and shipping instructions for these PK blood samples are presented in a separate laboratory manual provided by the Sponsor to the clinical site.

Cerebral Spinal Fluid for Assessment of Gantenerumab Concentration (for Patients Enrolled on the Basis of CSF Criteria Only)

For patients enrolled on the basis of CSF criteria and willing to perform lumbar puncture in the schedule of activities, an aliquot of CSF obtained by lumbar puncture, described in Section 4.5.6.2, will be allocated for the measurement of gantenerumab concentration. Samples from patients receiving placebo may not be assessed at once but will be retained for subsequent analysis if appropriate.

Unused sample material may also be used for the purposes of current assay improvement.

4.5.7 Electrocardiograms

Single 12-lead ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 5 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws, brain MRI scans, and lumbar puncture). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

The following should be recorded by the electrocardiograph machine: heart rate, QRS duration, and RR, PR, and QT intervals and transferred to the *Sponsor* database from the core laboratory.

4.5.8 Columbia–Suicide Severity Rating Scale

The C-SSRS (http://www.cssrs.columbia.edu) is an assessment tool used to assess the lifetime suicidality of a patient (C-SSRS at baseline) as well as any new instances of suicidality (C-SSRS since last visit). The structured interview prompts recollection of

suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual or potential lethality. The C-SSRS baseline will be collected at baseline and the C-SSRS since the last visit will be collected at subsequent visits as indicated in the schedule of activities (see Appendix 1).

The assessment will be completed by a certified C-SSRS rater after he or she interviews the patient and the patient's study partner during the study visit.

4.5.9 Brain Magnetic Resonance Imaging

MRI should be performed using 1.5-T or 3.0-T scanners, and wherever possible the same scanner should be used for an individual patient for the full duration of the study. MRI will be conducted at patient screening for safety monitoring, as a baseline measure of structural brain volumes, and as baseline information for the PET substudies (for the schedule of activities, see Appendix 1).

Where available, exploratory MRI techniques including rs-fMRI and DTI will also be acquired. In addition, the screening MRI will be used to help determine whether the exclusion criteria are met (e.g., number of microbleeds, presence of mass lesions, etc.).

MRI will be used during the study to help assess safety such as the occurrence of microbleeds or signs potentially indicative of inflammation or ARIA-E. Additional unscheduled MRI scans may be performed to better understand relevant CNS adverse events (such as increased confusion) occurring in the context of ARIA or to follow a sign that emerges at a scheduled scan; contrast agent may be used in such a case of follow-up MRI scans if administration of contrast agent is considered safe for the patient according to local standards. In addition, structural MRI (to assess whole brain and regional brain atrophy), fMRI, and DTI-MRI will be performed at multiple timepoints to determine potential treatment effects on MRI outcome measures (according to the schedule of activities).

MRI scans will include the following sequences:

- 3D T_1-weighted gradient recalled echo (GRE) scans
- T_2*-weighted GRE scans
- T_2-weighted FLAIR scans
- BOLD rs-fMRI, if available (to assess resting-state functional connectivity at investigative sites having the required software and sequences)
- DTI-MRI, if available (to assess fiber tract integrity)

For details on the specific imaging sequences and acquisition times required, refer to the MRI Manual.

MRI should not be performed unless at least 3 days have passed since a lumbar puncture. If an MRI and lumbar puncture are both scheduled for the same day, the MRI should be performed first.

All images (except BOLD fMRI and DTI-MRI) will be used to assess MRI inclusion and exclusion criteria.

MRI scans will be reviewed by a central MRI core laboratory, which will perform the diagnostic reads and assessment of MRI outcome measures. MRI scans should preferably be transferred to the central MRI core laboratory electronically. Data transfer from individual study sites to the central MRI core laboratory may take up to 7−10 days, if not done electronically. Upon receipt of the MRI scans from the study sites, the central MRI core laboratory will provide the diagnostic reads. MRI results must be made available to investigators prior to next dosing (refer to Section $5.1.3$ for additional details on MRI safety management).

MRI facility qualification and scan quality control will be performed by the central MRI core laboratory.

Additional instructions regarding the procedures for MRI scan acquisition and transmittal to the central reading facility can be found in the MRI Manual.

4.5.10 Healthy Volunteer Magnetic Resonance Imaging Scans for Site Qualification

As part of site qualification, one to two volunteers (preferably two) at each site should be recruited and scanned using the same machine and the same sequences to be used for site qualification before any patient is scanned in this study. The choice of healthy volunteers is at the discretion of the investigator and/or the imaging center, and the volunteer must provide written consent to take part in the scanning calibration. Volunteers must not have any contraindications for MRI scanning (evaluation per local procedures at the imaging site), and they will not be enrolled in the study or undergo any other assessments as part of the trial. If volunteer scans are acquired, then they will be reviewed for suitable image quality and used for qualitative comparison with additional scans with the same volunteer acquired after certain events as follows: at the time of a major upgrade to the site's scanner, any other event deemed significant enough to affect image quality, or per central reader guidance. This procedure will help ensure consistency in scanning quality over the duration of the study. Two volunteers are ideal in case one volunteer is no longer readily available for test scanning.

Additional instructions regarding the procedures for MRI facility qualification can be found in the MRI Manual.

4.5.11 Positron Emission Tomography Scan

A PET scan will be performed for confirmation of Aβ levels for eligibility purposes in patients (PET-enrolled patients). Three radioligands are be used for screening purposes: florbetapir F 18 (Amyvid™), flutemetamol F 18 (Vizamyl™), and florbetaben F 18 (Neuraceq™).

Screening PET scans must not be acquired prior, potentially exclusionary screening results are available in order to minimize radiation burden to patients. In order to allow sufficient flexibility for scheduling of the screening PET scan screening procedures (including central reading of the MRI scans) ideally should be completed within 2–3 weeks before the screening PET scan is required.

A positive PET scan using florbetapir F 18, flutemetamol F 18, or florbetaben F 18 acquired outside this study protocol may be permissible to confirm patient inclusion with Medical Monitor approval. Previously acquired PET scans must meet quality standards detailed in the PET Technical Operations Manual and must be centrally evaluated.

Detailed instructions regarding the procedures for PET scan methodology, including scanning procedures can be found in the PET Technical Operations Manual.

4.5.12 Optional Samples for Research Biosample Repository

4.5.12.1 Overview of the *Research Biosample* Repository

The RBR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be collected from retaining the residual samples remaining after the protocol-specified analysis has been performed on protocol-specified mandatory biomarker samples.

These residual samples will be retained from patients who give specific consent to participate in the optional study.

RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology

- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.12) will not be applicable at that site.

4.5.12.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to gantenerumab or AD:

- Leftover blood from Clinical Genotyping sample and clinical RNA sample, plasma biomarker sample, CSF samples and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing, or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.12.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR specimens, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.12.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.12.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be

provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study WN39658 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study WN39658.

4.5.12.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TIMING OF STUDY ASSESSMENTS

4.6.1 Screening and Pretreatment Assessments

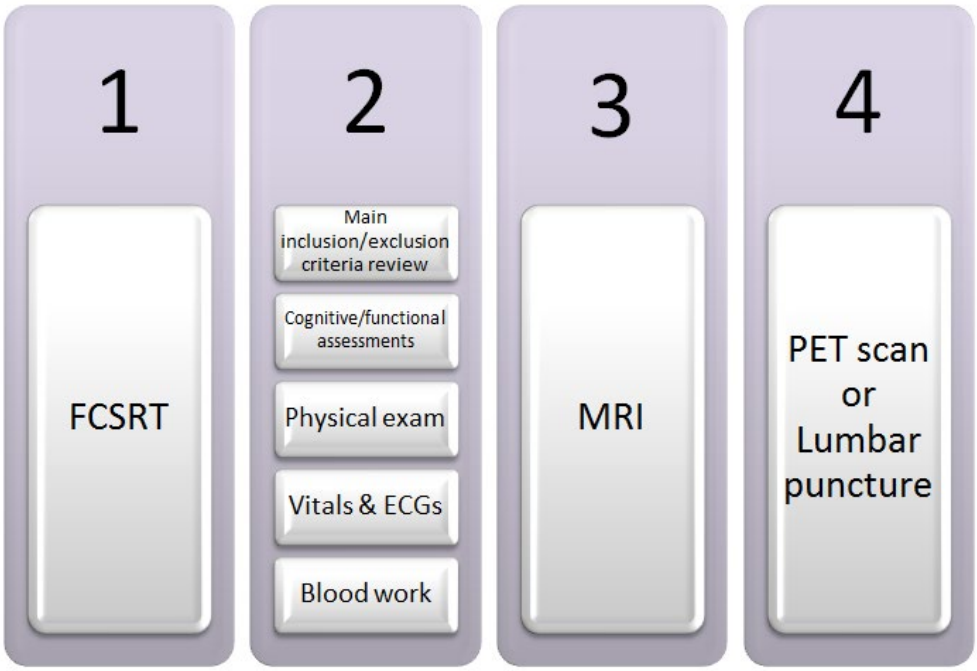
Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site. After providing written informed consent, patients who are willing to participate in the study will undergo all screening assessments within *12* weeks prior to the baseline visit, as detailed in the schedule of activities (see Appendix 1). Patients must fulfill all the entry criteria for participation in the study and the results must be available prior to the baseline visit.

The FCSRT *and MMSE assessments* may also be completed at prescreening. However, in this case, a separate prescreening consent would need to be signed and FCSRT *and MMSE* would not need to be repeated during the screening process. In case the patient would not qualify based on the FCSRT inclusion criteria, investigators have the option to repeat the FCSRT once after at least 6 months have elapsed if recruitment for the study is still ongoing.

In case of an abnormal laboratory or ECG result at screening that may normalize upon retest, investigators have the option to repeat the tests (prior to baseline and within the 8-week screening window) once to confirm the test results before randomizing a patient at baseline.

In rare cases in which a MRI scan needs to be repeated or any other unexpected delay due to logistical or technical reasons, the screening period may be extended by some days. Extending the screening period beyond *12* weeks must be approved by the Medical Monitor and should be for exceptional circumstances only; careful scheduling should remain a priority.

The recommended order of screening assessments is as follows:



ECG = electrocardiogram; FCSRT = Free and Cued Selective Reminding Test; MRI = magnetic resonance imaging; PET = positron emission tomography.

The recommended order of clinical assessments and rating scales at screening is shown below.

Patient Assessments	Study Partner Assessments
1. FCSRT (performed at prescreening or at screening) *10-min break (optional)* 2. *MMSE (performed at prescreening or at screening)* 3. *CDR (patient interview)*	CDR (study partner input)

CDR = Clinical Dementia Rating; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination.

CSF sampling, PET scan, and MRI scan at screening should be performed only once all other screening results are available and none exclude the patient from the trial.

If a patient does not qualify on the basis of applicable tests, the patient may be rescreened again after at least 3 months (6 months for FCSRT) have elapsed if recruitment for the study is still ongoing.

As noted in the exclusion criteria (see Section 4.1.2), patients may be rescreened after appropriate treatment if they were originally excluded for abnormal thyroid, folic acid, vitamin B-12, or HbA_{1c} results. Other laboratory tests that would exclude the patient may be repeated once (as an unscheduled laboratory assessment) if it is suspected that the abnormal result is transient and likely to be normal on repeat.

Patients may be rescreened if the protocol is amended such that they would satisfy the amended criteria and if recruitment for the study is still ongoing. In this case, all screening assessments must be repeated with the exception of lumbar puncture and prior PET scan if performed within the previous 12 months for this study and within eligible ranges. Given that *APOE* status will not change over time, there is no need to repeat clinical genotyping in case of rescreening.

Patients may be rescreened if there is a substantial change in the patient's condition (e.g., a disallowed medication was stopped) and if recruitment for the study is still ongoing and all eligibility criteria are met.

It is suggested that screening tests with the exception of the lumbar puncture, MRI scan, and PET scan be performed within 1 to 2 weeks of signing the Informed Consent Form (to allow adequate time for the remaining tests). As soon as all the results are available, and none exclude the patient from the trial, CSF collection and/or PET scan and MRI scan should be performed, if required.

It will take several days to receive the results of the MRI or CSF. On occasion the originally scheduled MRI or CSF collection day may need to be postponed and in the case of the MRI, it may need to be repeated. Therefore, the scheduling of these tests needs to be done carefully and should begin as soon as possible.

For patients enrolling on the basis of PET criteria, and for patients willing to participate in any of the PET substudies, scans can be obtained after all other screening results are available. For these patients, it is recommended that the MRI appointment should be scheduled to allow sufficient time for the PET scan to be performed and evaluated before the end of the screening period.

A positive PET scan using Amyvid™, Vizamyl™, or Neuraceq™ acquired outside this study may be permissible to confirm patient inclusion with Sponsor approval. Previously acquired PET scans must meet quality standards detailed in the PET Technical Operations Manual and must be centrally evaluated.

Roche may keep information about screening test results, medical history, and demographic information for all patients (including non-eligible patients) for future development of diagnostic tests related to Aβ, *APOE* genotype, and AD, as well as additional analyses.

4.6.2 Assessments at Baseline

In order to be randomized and to receive double-blind treatment, patients must have no significant change in medical, psychiatric, or neurological conditions or change in medication since screening. The recommended order of assessments and rating scales is as follows:

- Clinical assessments (e.g., CDR, MMSE, and ADAS-Cog), including all those that require study partner input, should be completed before any invasive safety assessments.
- Vital sign measurements, ECGs, blood draws for clinical laboratory assessments, PK, ADA, and plasma biomarker sampling, and urine samples are recommended to be conducted following scale assessments and must be performed prior to study drug administration.

The recommended order of clinical assessments/rating scales at baseline is as follows:

Patient Assessments	Study Partner Assessments
1. ADAS-Cog13	1. CDR (study partner input)
2. CDR (patient interview)	2. FAQ
10-min break (optional)	3. ADCS-ADL
3. MMSE	4. ZCI-AD
4. *Coding*	5. QoL-AD
5. Verbal Fluency Task	6. EQ-5D
10-min break (optional)	7. RUD-Lite
6. QoL-AD	8. NPI-Q
7. C-SSRS	

ADAS-Cog13 = Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living; CDR = Clinical Dementia Rating; C-SSRS = Columbia–Suicide Severity Rating Scale; EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; NPI-Q = Neuropsychiatric Inventory–Questionnaire; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

If assessments are split over 2 days, all safety assessments must be performed on the same day as the study drug administration.

4.6.3 Assessments during Treatment

Patients will receive up to 43 SC administrations of study drug over the course of 102 weeks. The final on-treatment efficacy and safety assessments are scheduled at Week 104, 2 weeks after the last dose.

The same recommended order of clinical assessments and rating scales as above for the baseline visit should be followed (omitting those that are not conducted per the schedule of activities; see Appendix 1).

Vital sign measurements, ECGs, blood draws for clinical laboratory assessments, PK, ADA, plasma biomarkers, and urine samples are recommended to be conducted following scale assessments and must be performed prior to study drug administration.

If assessments are split over 2 days, all safety assessments must be done on same day as the treatment administration.

On each dosing day, after all assessments prior to dosing have been completed (see the schedule of activities in Appendix 1), gantenerumab or matching placebo will be administered subcutaneously at room temperature. For the first four doses, patients should be observed for a minimum of 2 hours after dosing and then for a minimum of 1 hour after all remaining doses (i.e., Doses 5 and beyond). Patients should leave the study center after injections only if they appear to be tolerating the injections. When doses are to be administered remotely from the clinical sites, study drug administration may be performed only by qualified health care providers, as defined by local regulations, who must remain with the patients for a minimum of 1 hour after each injection and be equipped with rescue medications.

Rescue medications to treat anaphylactic and anaphylactoid reactions must be available at the site or at the dosing location for HN visits. Patients and their study partners will be alerted to watch for signs of anaphylactic and anaphylactoid reactions and to contact the study center as soon as possible if any such signs are noted.

Visits at which the patient receives study drug may take place within ± 7 days of the protocol-specified date for Q4W administration and ± 3 days of the protocol-specified date for Q2W administration per the schedule of activities in Appendix 1.

However, all visits should be scheduled as close as possible to the exact day. It is preferred that all assessments for a visit be performed on the same day, but if necessary, assessments may be performed over more than 1 day. Preferably, all clinical scales and assessments should be performed on the same day. Study drug administration should be performed only after all assessments and rating scales for the patient have been completed.

For sites and patients for whom this is practical, visits that require only dosing, vital sign measurements, urine pregnancy test, C-SSRS assessment, and adverse event assessment may be performed at an alternate location conducted by appropriate health care professionals.

Refer to Appendix 1 for the schedule of activities during the treatment period.

4.6.4 Procedures for New MRI Findings

In addition to any local reading according to local procedures and requirements, all MRI scans will be reviewed by an expert central reader within approximately 1 week of receipt and a report provided to the site. For the purposes of overall study relevant decisions and recommendations, including patient eligibility as well as for analysis, results from the expert central reader will be used. Any time the central reader identifies a new MRI finding the study center medical staff and the Sponsor will be rapidly notified (see Section 4.5.9).

Refer to Section 5.1.3 for instructions in the event of new MRI findings (ARIA-E and ARIA-H).

4.6.5 Assessments at Study Completion or Early Termination Visit

Patients who complete the double-blind treatment period (defined as completion of 102 weeks of study drug treatment) have to complete the final efficacy and safety assessment period 2 weeks following the last dose (Week 104), and subsequent 14-week and 50-week follow-up periods (Weeks 116 and 152, respectively).

All patients who withdraw from treatment or discontinue from the study early will be asked to return 2 weeks after the last dose of study drug in order to complete the early termination visit.

In addition patients who withdraw from treatment will be asked to return for collection of safety (except MRI) and limited efficacy data (i.e., the primary and secondary endpoints) at visits that have efficacy assessments (e.g., Week 52) per the schedule of activities until the end of the study (including Weeks 104, 116, and 152).

Autopsy reports, including cause of death, for all patients who die during the study (i.e., prior to the Week 50 follow-up visit) should be requested.

Refer to the schedule of activities to be performed at the study completion (Week 104 or early termination visit) in Appendix 1.

4.6.6 Follow-Up Assessments

Patients who complete the double-blind treatment period (defined as completion of 102 weeks of study drug treatment) and who are not willing to enroll in the OLE will be asked to return to the clinic 14 weeks and 50 weeks after the last dose of study drug for follow-up visits (Weeks 116 and 152, respectively).

Patients who withdraw from treatment will be asked to return for collection of safety (except MRI) and limited efficacy data (i.e., the primary and secondary endpoints) at visits that have efficacy assessments (e.g., Week 52) according to the schedule of activities until the end of the study (including Weeks 104, 116, and 152).

Patients who withdraw from study will only be asked to return 2 weeks after the last dose of study drug in order to complete the early termination visit.

When patients complete the treatment period or discontinue early, every effort should be made to ensure that the safety follow-up period and all related assessments are completed.

After the study completion or early termination visit, adverse events should be followed as outlined in Sections 5.5 and 5.6. Refer to the schedule of activities (see Appendix 1) for the list of assessments to be performed at the follow-up visits.

4.6.7 Unscheduled Assessments

Assessments at unscheduled visits should be determined by the investigator based on clinical relevance and appropriateness to the cause of the unscheduled visit. The schedule of activities in Appendix 1 allows for all assessments to be performed at unscheduled visits.

4.7 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Pregnancy
- Upon evidence of more than 15 ARIA-H, cumulatively
- Any disseminated leptomeningeal hemosiderosis

All patients who withdraw from treatment will be asked to return 2 weeks after last dose in order to complete the early termination visit *assessments*.

In addition, patients who withdraw from treatment will be asked to return for collection of safety (except MRI), and limited efficacy data (i.e., the primary and secondary endpoints) according to the schedule of activities until the end of the study (including Weeks 104, 116, and 152).

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

4.7.2 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Study termination or site closure
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance with the study and/or study procedures, defined as missing more than three consecutive dose administrations *(with Q4W dosing regimen) or more than six consecutive dose administrations (with Q2W dosing regimen)* because of non–safety-related reasons or more than *half of the dosing* visits in a calendar year

All patients who discontinue from the study early will be asked to return 2 weeks after last dose in order to complete the early termination visit.

Patient should be informed of circumstances under which their participation may be terminated by the investigator without the patient's consent. Any administrative or other reasons for withdrawal must be explained to the patient.

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn.

Patients who withdraw from the study will not be replaced.

4.7.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Futility analyses suggesting that treatment with gantenerumab is likely not effective.
- Sponsor determines it is the best interest of the patients.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.7.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Gantenerumab is not yet approved, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with gantenerumab in completed and ongoing studies. The identified risks for gantenerumab are outlined below. Please refer to the Gantenerumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for imaging-related abnormalities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Gantenerumab

5.1.1.1 Amyloid-Related Imaging Abnormalities

To date, clinical experience with gantenerumab reveals that ARIA events are dose-dependent and *APOE* ε4 dependent. These events are manageable with MRI monitoring and dose intervention algorithms. In addition, in case of clinical symptoms, the use of IV glucorticosteroids may be considered.

Rules for management of patients who develop ARIA-E or ARIA-H are provided in Appendix 6.

5.1.1.2 Injection-Site Reactions

Gantenerumab may cause a reaction when given as an SC injection. In studies with gantenerumab, the most common events occurring more frequently with gantenerumab than with placebo were local ISRs, such as reddening of the skin. The events were of mild intensity and resolved in most of the case without any treatment.

Detailed information on the characteristic signs and *symptoms* of *injection-site reactions* (e.g., erythema, pruritus) *will* be recorded on the *dedicated* eCRF *page.*

No gantenerumab-related immunogenicity reactions of major clinical relevance have emerged to date. Patients should be monitored for and alerted to the risk of any symptoms of hypersensitivity reactions.

5.1.2 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

5.1.3 Management of Patients Who Experience Selected Adverse Events

Patients will undergo brain MRI examinations prior to every dose increase (pre-uptitration MRI scans) and according to the schedule of activities once the target dose is achieved. The pre-uptitration MRI scans will determine eligibility for the next uptitration dose. Patients will be eligible for uptitration if there are no new ARIA-E, if the ARIA-E is resolved (BGTS=0), and if the criteria for discontinuation because of ARIA-H have not been met. In exceptional cases of ARIA-E that has significantly decreased and has being stable without associated clinical symptoms for several months as defined by the central reader, uptitration may be resumed.

In addition, the following dose adjustment and discontinuation rules for MRI findings will apply:

- In case of asymptomatic ARIA-E $\geq$1 and $<$4 BGTS: Continue study drug at the same dose level (i.e., do not uptitrate) and repeat MRI 4 weeks later.

  As long as BGTS is $<$4 and $\geq$1, continue study drug at the same dose level and continue MRI monitoring at 4-week intervals until the event resolves. When ARIA-E resolves, resume uptitration and MRI monitoring according the schedule of activities.

  If BGTS $\geq$4 or symptoms develop, refer to the rule below.

- In case of occurrence of symptoms in the presence of ARIA-E (any size) or asymptomatic ARIA-E with ≥4 BGTS: Temporarily interrupt study drug (but continue all assessments per schedule of activities) and implement MRI monitoring performed at 4-week intervals until symptoms and ARIA resolve.

  When symptoms and ARIA-E resolve, reintroduce study drug at the next scheduled dosing visit, at the same dose given at the time the event was detected and perform an MRI scan after the first dose for patients on Q4W regimen and after the second dose for patients on the Q2W regimen.

  If no new ARIA-E is detected, resume uptitration and obtain an MRI scan per the titration schedule. For patients on the Q2W regimen, perform another MRI scan 3 months after study drug reintroduction.
- Any recurrence of ARIA-E: Treat using the same procedures as for the first event (based on symptoms and BGTS).
- Patients who develop >15 ARIA-H cumulatively will be discontinued from study drug (the cumulative number should not include any disseminated leptomeningeal hemosiderosis, i.e., up to 3 focal leptomeningeal hemosiderosis; a focal leptomeningeal hemosiderosis is counted as an ARIA-H).
- In cases where both ARIA-E and ARIA-H occur, the most conservative approach should be followed.
- A PK sample will be obtained once the site becomes aware of the occurrence or worsening of ARIA-E or ARIA-H that meet the discontinuation criteria (e.g., an unscheduled visit).
- The investigators may choose to perform additional MRI monitoring for ARIA at any time.
- MRI monitoring of ARIA findings should be conducted at approximately 4-week intervals.

The iDMC will review the incidence of ARIA in an unblinded manner and may recommend adjustment of dosing regimen and/or ARIA management for the overall study population or for a specific *APOE* ε4 genotype.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.12)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe; the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.8)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.2.4 Selected Adverse Events

Data on associated symptoms and safety MRI scans will be collected for the following selected adverse events:

- ARIA-E: ARIAs suggestive of vasogenic edema and sulcal effusions
- ARIA-H: ARIAs suggestive of microhemorrhages and/or hemosiderin deposits

Please refer also to Section 5.3.5.1 for further details how to report ARIA events.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4). *The investigator is also responsible for reporting medical device complaints (see Section 5.4.4).*

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

In addition, after administration of a PET ligand, but prior to initiation of study drug, the following adverse events should be reported:

- *All adverse events (serious or non-serious) believed to be related to a PET ligand*
- *All serious adverse events occurring within 48 hours of PET ligand administration regardless of relatedness to the PET ligand*

For reporting of serious adverse events, see Section 5.4.2 for instructions. For non-serious PET ligand adverse events, a PET ligand specific non-serious adverse event reporting paper form should be completed and submitted to the Sponsor or its designee by scanning and emailing the form using the email address provided on the form.

After initiation of study drug, all adverse events will be reported until *the patient's last visit (including long-term follow-up visits).*

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

Table 3 provides guidance for assessing adverse event severity.

Table 3 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 ARIA Findings

Not every ARIA finding qualifies as an adverse event. An ARIA finding must be reported as an adverse event if it meets any of the following criteria:

- Is *symptomatic (i.e.,* accompanied by CNS symptoms*), and/or*
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)*, and/or*
- Is *otherwise* clinically significant in the investigator's judgment

Any accompanying symptoms should also be captured as separate adverse events.

It is the investigator's responsibility to review all ARIA findings.

Observations of the same clinically significant ARIA finding should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.2 Injection-Related Reactions

Individual signs and symptoms of injection-*site reactions (e.g., erythema, pain)* should be *reported on the Injection-Site Reaction eCRF. The overall diagnosis of injection-site reaction should be* captured on the Adverse Event eCRF. *Systemic reactions* should be recorded *as a single diagnosis.*

5.3.5.3 Diagnosis versus Signs and Symptoms

For adverse events, other than injection-related reactions (see Section 5.3.5.2), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.4 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.5 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes

more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.6 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5× ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.7 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.8 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.9 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of AD.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed to progression of AD, "Alzheimer's disease progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.10 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.11 Lack of Efficacy or Worsening of Alzheimer's Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is because of disease progression, it should be reported as an adverse event.

5.3.5.12 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization due to expected progression of underlying disease
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

5.3.5.13 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a study drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.14 Clinical Outcome Assessment Data

Adverse event reports will not be derived from clinical outcome assessment (COA) data by the Sponsor, and safety analyses will not be performed using COA data. *Sites are not expected to review the COA data for adverse events.*

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information

- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor: [redacted], *M.D. (Primary)*
Telephone No.:
Mobile Telephone No.:

Medical Monitor: [redacted], M.D. *(Secondary)*
Telephone No.:
Mobile Telephone No.:

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.

In addition, the following serious adverse events should be reported after administration of a PET ligand and prior to initiation of study drug:

- *All serious adverse events believed to be related to the PET ligand*
- *All serious adverse events occurring within 48 hours of the PET ligand administration, regardless of relatedness to the PET ligand.*

The paper *Clinical Trial* Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until *the patient's last visit (including long-term follow-up visits)*. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 16 weeks after the last dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 *Reporting Requirements for Medical Device Complaints*

The investigator must report all medical device complaints (e.g., devices for study drug administration) to the Sponsor. The investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the pharmacy manual for further details). If the medical device results in an adverse event to the study patient, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously

communicate possible new safety findings to investigators, IRBs, Ecs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document: the Gantenerumab Investigator's Brochure.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The purpose of this study is to investigate the treatment effect of gantenerumab relative to placebo. The primary efficacy analysis will be based on an intent-to-treat (ITT) population, which will include all randomized patients during the global enrollment phase, with patients grouped according to their randomly assigned treatment.

Approximately *760* patients will be randomized in the global enrollment phase of this study. An increase in sample size may be considered in case of changes to sample size assumptions based on blinded data review or factors external to the study.

If at least 1 patient is enrolled *at sites* in *mainland* China*, Hong Kong, and Taiwan that are recognized by the CFDA* during the global enrollment phase, additional patients may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in the China.

The primary analyses of this study will include patients enrolled during the global enrollment phase; data from patients enrolled during the China extension will not be included in the primary analyses.

6.1 DETERMINATION OF SAMPLE SIZE

Determination of sample size is based on patients enrolled in the global enrollment phase. In this study, approximately *760* patients will be enrolled and randomized in 1:1 ratio to each treatment arm (gantenerumab or placebo) during the global enrollment phase. A sample size increase may be considered if factors external to the study or blinded study data analysis would warrant a change to the sample size assumption.

Additional patients may be randomized during the China extension if at least 1 patient is enrolled *at sites in mainland China, Hong Kong, and Taiwan that are recognized by the CFDA* during the global enrollment phase.

The estimated sample size required to demonstrate efficacy with regard to CDR-SOB is based on the following assumptions:

- The mean change in the CDR-SOB from baseline to Week 104 is *2.5* points in the placebo arm
- A common standard deviation across treatment arms for change of approximately *2.97* from baseline to Week 104 in the CDR-SOB
- Gantenerumab has a true effect of a 30% relative reduction in deterioration of CDR-SOB

Based on these assumptions*, and using a student's T-test with equal variance,* a sample size was calculated for 80% power to detect a true treatment effect of 30% relative reduction in deterioration of CDR-SOB at a two-sided α of 0.05.

Uncertainties on parameters affecting the power (e.g., dropout rate, study drug discontinuation rate, standard deviation, and placebo decline) were assumed to be equivalent to a drop-in sample size of up to around 35% and were corrected for accordingly. This calculation leads to a total of 760 patients in the study.

The sample size may be increased from *760* up to *1140* patients (*570* patients per arm). *The* decision whether to increase sample size will be based on a blinded assessment of pooled CDR-SOB change from baseline. Further details will be described in the Statistical Analysis Plan (SAP). The assessment will be performed by the Sponsor at a specified timepoint. *The sponsor will remain blinded.* The sample size will not be reduced on the basis of this assessment. Other factors external to the study may also trigger a decision to increase sample size.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, patient disposition, and incidence of protocol deviations will be summarized for the ITT population according to the randomly assigned treatment arms.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (such as age, sex, race, disease stage, *APOE* ε4 status, use and non-use of background therapy for AD) will be summarized descriptively for the ITT population, grouped according to the assigned treatment arm.

Descriptive summaries of continuous data will present the mean, standard deviation, median, and minimum and maximum. Descriptive summaries of discrete data will include frequencies expressed in terms of number and percentage of patients.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will use the ITT population, with patients grouped according to the treatment assigned at randomization.

6.4.1 Primary Efficacy Endpoint

The primary efficacy outcome measure is the change in CDR-SOB from baseline (Day 1) to Week 104. For the primary outcome measure, the difference in mean change from baseline to Week 104 between gantenerumab-treated patients and placebo-treated patients will be estimated. The analysis will use the ITT population, with patients grouped according to the treatment assigned at randomization. A mixed model repeated measures (MMRMs) analysis adjusting for baseline CDR-SOB score, disease stage, *APOE* ε4 status, geographic region and use of AD medication at baseline will be used to estimate the mean change from baseline to Week 104 for the primary endpoint.

The model will include the change from baseline in CDR-SOB as the dependent variable. The effects in the model will include baseline CDR-SOB score, disease stage, *APOE* ε4 status, geographic region, use of AD medication at baseline, treatment group, visit, and treatment-by-visit interaction. Visit week will be treated as the repeated variable within a patient. Disease stage, *APOE* ε4 status, geographic region, background medication at baseline, patient, treatment, and visit week will be treated as class variables. An unstructured variance-covariance structure will be applied to model the within-patient errors; in case of non-convergence, compound symmetry will be used.

The difference in the change from baseline of the patients randomized to gantenerumab from patients randomized to placebo will be estimated at each timepoint. The 95% CI and p-value for treatment difference will be presented.

All efforts will be made to minimize missing data. The Sponsor plans to request patients who discontinue early from study treatment to return for collection of safety and limited efficacy data (i.e., the primary and secondary efficacy endpoints) until Week 104. To explore the robustness of MMRM results for the primary efficacy conclusions sensitivity analyses (e.g., using multiple imputation and pattern mixture models) will be performed. Descriptive summaries of the number of patients with missing data, the timing, and reasons for discontinuation from the study will also be provided by treatment group.

Additional details will be documented in the SAP.

6.4.2 Secondary Efficacy Endpoints

The absolute change from baseline in the continuous secondary efficacy endpoints listed in Section 2, Table 2 (including cognition/function endpoints, global endpoints, disease pathology biomarkers, and endpoints measuring other AD symptoms and effects) will be analyzed using an MMRM analysis model similar to that described above for the primary efficacy endpoint.

For time-to-event endpoints, the Kaplan-Meier method will be used to estimate the median time-to-event for each treatment arm. The Cox proportional hazard model stratified by the randomization stratification factors will be used to estimate the hazard ratio and its 95% CI. The two-sided log-rank test, stratified by the randomization

stratification factors, will be used to perform hypothesis testing for assessing treatment difference between the two treatment arms at a 5% significance level.

In order to protect the overall type I error rate for the study when incorporating the hypothesis testing of the primary endpoint *and secondary endpoints* into the analysis, the fixed sequence testing procedure (Westfall and Krishen 2001) will be used to adjust for multiple comparisons. The first *endpoint that* will be tested *is*:

- Change from baseline to Week 104 in CDR-SOB

The order of testing for other secondary endpoints will be defined in the SAP.

The treatment difference in the primary endpoint (the change from baseline to Week 104 in the CDR-SOB) will be tested at a two-sided 5% overall significance level. The overall significance level will be maintained using the O'Brien-Fleming boundary. If this test result is statistically significant at either the interim or the final analysis, the secondary endpoints will be tested for significance in the predefined order *as specified in the SAP*. If any test result is not statistically significant, testing of the subsequent endpoints will not occur.

6.4.3 Exploratory Efficacy Analyses

Subgroup analysis of efficacy results will be performed for subgroups defined by age, sex, race, stage of disease (prodromal AD vs. mild AD), *APOE* ε4 status, geographic region, use and non-use of background therapies for AD, and other clinically relevant factors at baseline.

6.4.4 Pharmacodynamic and Exploratory Biomarker Analyses

PD and exploratory biomarker endpoints will be analyzed using descriptive statistics, subgroup analysis, or statistical models if appropriate. For longitudinally measured endpoints, the change from baseline and the difference between patients randomized to gantenerumab and patients randomized to placebo will be estimated if appropriate. Exploratory biomarkers may be reported separately.

6.5 SAFETY ANALYSES

The safety-analysis population will include all randomized patients who receive at least one dose of study drug, with patients grouped according to the treatment actually received, as defined in the SAP.

- Incidence, nature, and severity of MRI safety findings: ARIA-E and ARIA-H
- Incidence, nature, and severity of serious adverse events
- Incidence, nature, and severity of adverse events
- Incidence of adverse events of special interest
- Incidence of treatment discontinuations due to adverse events

- Mean changes in clinical laboratory tests from baseline over time; incidence of treatment-emergent abnormal laboratory values and abnormal laboratory values reported as adverse events
- Mean change in ECG assessments from baseline over time and incidence of abnormal ECG assessments
- Physical and neurologic examination abnormalities
- Mean change in vital signs (blood pressure, pulse rate) from baseline over time and incidence of abnormal vital sign measurements
- Changes in CSSR-S scores from baseline over time
- Number and proportion of ADA-positive and ADA-negative patients during both the treatment and follow-up periods will be summarized by treatment group

6.6 PHARMACOKINETIC ANALYSES

Plasma concentration data for gantenerumab will be tabulated and summarized. Descriptive summary statistics will include the arithmetic mean, median, range, SD, and coefficient of variation, as appropriate. Because a sparse PK sampling design is being used, population (non-linear mixed-effects) modeling will be used to analyze the dose concentration–time data of gantenerumab. Information from other clinical studies may be incorporated to establish the PK model. The selection of parameters and the derivation of individual measures of exposure, such as AUC, C_{max}, and trough serum concentration, will depend on the final PK model used for this analysis. The results of this modeling analysis may be reported separately from the clinical study report.

CSF concentrations of gantenerumab will be tabulated and summarized as appropriate from the substudy.

The influence of background medication on the pharmacokinetics of gantenerumab will be explored and, if appropriate, concentration–effect relationships may be assessed post hoc for PD, efficacy, or safety measures.

Additional PK analyses will be conducted as appropriate and may be reported separately from the clinical study report.

6.7 INTERIM ANALYSIS

6.7.1 Planned Interim Analysis

An interim analysis for efficacy and futility is to be conducted approximately 24 months after 50% of the targeted study enrollment has been reached.

An independent data coordinating center will be responsible for the interim analyses and study results will only be reviewed by the iDMC. The Sponsor will remain blinded.

The iDMC may recommend stop for futility if the failure criterion is met. The failure criterion will represent a low probability of a positive study outcome given the data observed at the time of interim analysis. The failure criterion will be prespecified in the iDMC SAP.

In contrast, the iDMC may "declare the study positive for overwhelming efficacy" if the study meets the success criterion on the primary endpoint. The success criterion is defined as the p-value threshold determined by standard Lan and DeMets methodology (1983) for group sequential design using the O'Brien-Fleming boundary function. If the study continues beyond the interim analysis, the critical value at the final analysis will be adjusted accordingly.

6.7.2 Optional Interim Analysis

Based on availability of information pertaining to gantenerumab or other compounds with similar mode of action that may emerge during the course of this study, the Sponsor may choose to conduct an additional interim analysis for futility and/or efficacy beyond the interim analysis mentioned above.

An independent data coordinating center will be responsible for the interim analyses and study results will only be reviewed by the iDMC. The Sponsor will remain blinded.

Details of the interim analyses, including the decision to conduct the optional interim analysis, the rationale, timing, and statistical details for the analyses (such as the data that would be reviewed by the iDMC and futility or efficacy thresholds) will be documented in a SAP, and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.

6.8 CHINA EXTENSION ANALYSIS

The objective of the China extension and the China subpopulation analyses is to assess the treatment effects of gantenerumab in a population of patients *enrolled at sites in mainland China, Hong Kong, and* Taiwan *that are recognized by the CFDA and* to investigate the consistency in treatment effect between the China subpopulation and the global population for the purpose of registration in China.

All patients enrolled in the global enrollment phase in China will be included in the primary analysis. The analysis of the China extension will be conducted after the end of China extension and will be reported separately from the primary analysis and at a subsequent point in time.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of

eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. All electronic data from external vendors will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

COA data will be collected through the use of an electronic device (tablet) provided by a vendor. Some COA data may be audio recorded for quality assurance purposes. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR, Part 11).
The electronic data are available for view access only via secure access to an online Web portal. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC CLINICAL OUTCOME DATA

Patients, study partners, and appropriate site staff will use an electronic device (tablet) to capture COA. For some COA, audio recordings may be used for quality assurance purposes. All data will be transmitted via Web automatically after entry into a centralized database maintained by the electronic device vendor.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and

machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site’s computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic COA data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or *Home* Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the

local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and

data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

The overall procedures for quality assurance of clinical study data are described in the Roche standard operating procedures. This study will be sponsored by F. Hoffmann-La Roche Ltd. Roche will provide clinical operations oversight, site monitoring and management, data management support, and medical monitoring.

Study drug distribution may occur through an IxRS (see Section 4.2). Central facilities may be used for study assessments (i.e., ECG, lumbar puncture, specified laboratory tests, PK, rating scales, and MRI and PET imaging, as applicable).

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

Table 1: Schedule of Activities (Week –*12* to Week 32; Dose Escalation with Q4W Administration)

Assessment/Procedure	*Prescreen* & Screening	Baseline	Dose Escalation Period									Unsched Visit
	Weeks –*12* to –1	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	
Dose Number		1 [a]		2	3	4	5 [b]	6 [b]	7 [a]	8 [b]	9 [b]	
Dose level in milligrams (mg)		*120*		*120*	*120*	*255*	*255*	*255*	*510*	*510*	*510*	
Informed consent(s) [c]	x											
Review of inclusion and exclusion criteria	x	B										
Medical history, personal status, and demographics	x											
Weight *and height* [t]	x											x
Clinical genotyping samples	x											
Clinical RNA samples	x											
Urinalysis [d]	x											
Urine sample for drugs of abuse [e]	x											
Coagulation (PT)	x											
Viral serology (HIV, hepatitis B, and hepatitis C)	x											
FCSRT	*P* [f]											
12-Lead electrocardiogram [g]	x	B				B			B			x
PK plasma sample [h]		B	x						B			x
ADA sample		B							B			x
Serum chemistry [i] and hematology [j]	x	B							B			x

Appendix 1
Schedule of Activities (cont.)

Table 1: Schedule of Activities (Week –*12* to Week 32; Dose Escalation with Q4W Administration) (cont.)

Assessment/Procedure	*Prescreen* & Screening	Baseline	Dose Escalation Period									Unsched Visit
	Weeks –*12* to –1	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	
Dose number		1 [a]		2	3	4	5 [b]	6 [b]	7 [a]	8 [b]	9 [b]	
Dose level in milligrams (mg)		*120*		*120*	*120*	*255*	*255*	*255*	*510*	*510*	*510*	
Plasma biomarker sample	x								B			x
Complete physical examination (includes neurological systems) [k]	x											x
Limited physical examination [l]									B			x
MRI scan [m, n]	x [o]					B			B			x
CSF *and matching serum* sampling [m, p] or PET scan [m, p]	x											
CDR	P&SP	P&SP							P&SP			P&SP
ADAS-Cog13		P							P			P
Verbal Fluency Task		P							P			P
Coding		*P*							*P*			*P*
ADCS-ADL		SP							SP			SP
FAQ		SP							SP			SP
MMSE	P *f*	P							P			P
EQ-5D		SP							SP			SP
QoL-AD		P&SP							P&SP			P&SP
ZCI-AD		SP							SP			SP
RUD-Lite		SP							SP			SP
NPI-Q		SP							SP			SP

Appendix 1
Schedule of Activities (cont.)

Table 1: Schedule of Activities (Week –*12* to Week 32; Dose Escalation with Q4W Administration) (cont.)

Assessment/Procedure	*Prescreen* & Screening	Baseline	Dose Escalation Period									Unsched Visit
	Weeks –*12* to –1	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	
Dose number		1 [a]		2	3	4	5 [b]	6 [b]	7 [a]	8 [b]	9 [b]	
Dose level in milligrams (mg)		*120*		*120*	*120*	*255*	*255*	*255*	*510*	*510*	*510*	
C-SSRS BL/SLV		P							P			P
Vital signs [q]	x	B	B	B	B	B	B	B	B	B	B	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [r]	x	B		B	B	B	B	B	B	B	B	x
Study drug administration [h, s]		x		x	x	x	x	x	x	x	x	

ADAS-Cog13=Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL=Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR=Clinical Dementia Rating; CSF=cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D=EuroQol-Five Dimensions; FAQ=Functional Activities Questionnaire; FCSRT=Free and Cued Selective Reminding Test; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; NPI-Q=Neuropsychiatric Inventory–Questionnaire; PET=positron emission tomography; PK=pharmacokinetic; Prescreen=prescreening; Q4W=every 4 weeks; QoL-AD=Quality of Life–Alzheimer's Disease; RBR=Research Biosample Repository; RUD-Lite=Resource Utilization in Dementia–Lite; SC=subcutaneous; Unsched=unscheduled; Wk=week; ZCI-AD=Zarit Caregiver Interview–Alzheimer's Disease.

B=before study drug administration; P=patient completion; P&SP=patient and study partner completion; SP=study partner completion.

Notes: The visit window is ±7 days for dosing days. Patients should return to initial planned schedule per randomization for subsequent visits.

In case of rescreening a patient, all screening assessments must be repeated other than the lumbar puncture and amyloid PET testing if performed within the previous 12 months for this study and are within the eligible ranges. In addition, clinical genotyping will not need to be repeated in case of rescreening.

[a] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first, and within 1 week prior to the first dose at baseline. All safety assessments (e.g., vital signs, blood tests, and ECGs) should be completed on the day of dosing.

[b] Visit suitable for home administration of gantenerumab.

Appendix 1
Schedule of Activities (cont.)

Table 1: Schedule of Activities (Week –*12* to Week 32; Dose Escalation with Q4W Administration) (cont.)

[c] Patients participating in the optional prescreening period must provide written consent before any study-specific prescreening assessments are performed. If patient is eligible and decides to participate in the screening assessments, he or she will need to provide new written consent.

[d] Performed at the site by dipstick for blood, protein, glucose, and pH.

[e] Urine samples will be analyzed for the presence of the following drugs: amphetamine, benzodiazepines, cannabinoids, opiates, cocaine, barbiturates, and methadone.

[f] *Can be done at prescreening or at screening. There is no need to repeat the test at screening if* performed at prescreening.

[g] Electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 5 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws, brain MRI scans, and lumbar puncture). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

[h] Accurate recording of the date and time of study drug administration and PK sampling is critical.

[i] Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). During the screening period (Week –1 to Week –8), hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[j] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelets, basophils, eosinophils, lymphocytes, monocytes, neutrophils, and WBC–other total counts.

[k] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

[l] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in patient notes.

[m] CSF *and matching serum* sampling, and PET and MRI scans at screening should be performed once all other screening results are available and none exclude the patient from the study.

[n] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[o] Includes resting-state functional MRI and DTI outcome measures where available.

[p] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters. For post-baseline visits, lumbar puncture *as well as serum sampling* should be performed prior to dosing. Only one method (CSF or PET) confirming amyloid is necessary for all patients.

Appendix 1
Schedule of Activities (cont.)

Table 1: Schedule of Activities (Week *–12* to Week 32; Dose Escalation with Q4W Administration) (cont.)

[q] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the patient is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined by radial pulse and will be recorded as beats per minute. Pulse rate should be counted for a minimum of 20 seconds at each assessment.

[r] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[s] Study drug administration should be performed only after all assessments/rating scales for the patient are completed (unless indicated otherwise). Study drug will be administered to patients by SC injection. Patients should be observed up to 2 hours after dosing. After the fourth injection visit, the observation time may be reduced to 1 hour. Study personnel *preparing and* administering study drug must not be involved with any efficacy assessments or safety evaluations.

[t] *Height measured at screening only.*

Appendix 1
Schedule of Activities (cont.)

Table 2: Schedule of Activities (Week 36 to the End of Study: *510* mg Q2W)

Assessment/Procedure	Treatment Period										Final Efficacy and Safety Assessments	Follow-Up Period for Patients Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
	Wk 36	Wk 38	Wk 40	Wk 41	Wk 42–50	Wk 52	Wk 54–74	Wk 76	Wk 78–102	Wk 103	Wk 104 [a, b]	Wk 116	Wk 152		
Dose number	10	11	12		13–17 [c]	18 [a]	19–29 [c]	30 [a]	31–43 [c]						
Dose level in milligrams (mg)	*510*	*510*	*510*		*510*	*510*	*510*	*510*	*510*						
12-Lead ECG						B		B			x	x		x	x
PK plasma sample [d]				x (Site visit)		B		B		x (Site visit)		x	x	x	x
ADA sample						B		B				x	x	x	x
Clinical RNA sample											x				
Serum chemistry [e] and hematology [f]						B		B			x	x	x	x	x
Plasma biomarker sample						B					x			x	x
Complete physical examination (including neurological systems) [g]											x			x	x
Limited physical examination [h]						B		B							x
Weight											x			x	x
MRI scan [i]	B				Wk 48 [j]		Wk 60	B			x [j]			x [j]	x
CSF [k] *and matching serum* sampling (for patients enrolled based on CSF eligibility criteria only)						x					x			x [k]	
CDR						P&SP		P&SP			P&SP		P&SP	P&SP	P&SP

Appendix 1
Schedule of Activities (cont.)

Table 2: Schedule of Activities (Week 36 to the End of Study: *510* mg Q2W) (cont.)

Assessment/Procedure	Treatment Period										Final Efficacy and Safety Assessments	Follow-Up Period for Patients Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
	Wk 36	Wk 38	Wk 40	Wk 41	Wk 42–50	Wk 52	Wk 54–74	Wk 76	Wk 78–102	Wk 103	Wk 104 [a, b]	Wk 116	Wk 152		
Dose number	10	11	12		13–17 [c]	18 [a]	19–29 [c]	30 [a]	31–43 [c]						
Dose level in milligrams (mg)	*510*	*510*	*510*		*510*	*510*	*510*	*510*	*510*						
ADAS-Cog13						P		P			P		P	P	P
Verbal Fluency Task						P		P			P		P	P	P
Coding						*P*		*P*			*P*		*P*	*P*	*P*
ADCS-ADL						SP		SP			SP		SP	SP	SP
FAQ						SP		SP			SP		SP	SP	SP
MMSE						P		P			P		P	P	P
EQ-5D						SP		SP			SP			SP	SP
QOL-AD						P&SP		P&SP			P&SP			P&SP	P&SP
ZCI-AD						SP		SP			SP			SP	SP
RUD-Lite						SP		SP			SP			SP	SP
NPI-Q						SP		SP			SP			SP	SP
C-SSRS BL/SLV						P		P			P			P	P
Vital signs [l]	B	B	*B*		B	B	B	B	B		x	x	x	x	x
Concomitant medications	x	x	*x*	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	*x*	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Activities (cont.)

Table 2: Schedule of Activities (Week 36 to the End of Study: *510* mg Q2W) (cont.)

Assessment/Procedure	Treatment Period										Final Efficacy and Safety Assessments	Follow-Up Period for Patients Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
	Wk 36	Wk 38	Wk 40	Wk 41	Wk 42–50	Wk 52	Wk 54–74	Wk 76	Wk 78–102	Wk 103	Wk 104 [a, b]	Wk 116	Wk 152		
Dose number	10	11	12		13–17 [c]	18 [a]	19–29 [c]	30 [a]	31–43 [c]						
Dose level in milligrams (mg)	*510*	*510*	*510*		*510*	*510*	*510*	*510*	*510*						
Urine pregnancy test [m]	B	B	*B*		B	B	B	B	B		x	x		x	x
Study drug administration [d, n]	x	x	*x*		x	x	x	x	x						

ADAS-Cog13=Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL=Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR=Clinical Dementia Rating; CSF=cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D=EuroQol-Five Dimensions; FAQ=Functional Activities Questionnaire; FCSRT=Free and Cued Selective Reminding Test; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; NPI-Q=Neuropsychiatric Inventory–Questionnaire; OLE=open-label extension; PET=positron emission tomography; PK=pharmacokinetic; Q2W=every 2 weeks; QoL-AD=Quality of Life–Alzheimer's Disease; RBR=Research Biosample Repository; RUD-Lite=Resource Utilization in Dementia–Lite; SC=subcutaneous; Unsched=unscheduled; Wk=week; ZCI-AD=Zarit Caregiver Interview–Alzheimer's Disease.

B=before study drug administration; P=patient completion; P&SP=patient and study partner completion; SP=study partner.

Notes: The visit window is ±3 days for dosing days. Patients should return to initial planned schedule per randomization for subsequent visits.

[a] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vitals, blood tests, and ECGs) should be completed on the day of dosing.

[b] Transition to OLE study for patients who are eligible to participate.

[c] Visit suitable for home administration of gantenerumab.

[d] Accurate recording of the date and time of study drug administration and PK sampling is critical.

Appendix 1
Schedule of Activities (cont.)

Table 2: Schedule of Activities (Week 36 to the End of Study: *510* mg Q2W) (cont.)

[e] Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). At Week 52 and Week 104, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[f] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

[g] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

[h] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in patient notes.

[i] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[j] Includes resting-state functional MRI and DTI outcome measures, where available.

[k] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For patients enrolling based on CSF eligibility criteria, CSF *and matching serum* samples are mandatory at Week 104 and optional at Week 52; the need of CSF collection at early termination visit will be discussed on a case-by-case basis with the Medical Monitor.

[l] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the patient is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined by radial pulse and will be recorded as beats per minute. The pulse rate should be counted for a minimum of 20 seconds at each assessment.

[m] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[n] Study drug administration should be performed only after all assessments and rating scales for the patient are completed (unless indicated otherwise). Study drug will be administered to patients by subcutaneous injection (full details are provided in the pharmacy manual). Patients should be observed for up to 2 hours after dosing. After the fourth injection visit, this observation time may be reduced to 1 hour. Study personnel *preparing and* administering study drug must not be involved with any efficacy assessments or safety evaluations.

Appendix 2
National Institute on Aging/Alzheimer's Association Criteria for Mild Alzheimer's Disease

NIA/AA Category	Description
Probable dementia: core clinical criteria Meets criteria for dementia described earlier in the text, and, in addition, has the following characteristics:	A. Insidious onset: Symptoms have a gradual onset over months to years, not sudden over hours or days B. Clear-cut history of worsening of cognition by report or observation; and C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories: 1. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text. 2. Non-amnestic presentations • Language presentation: The most prominent deficits are in word finding, but deficits in other cognitive domains should be present. • Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present. • Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present. D. The diagnosis of probable AD dementia should not be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or non-fluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

AD = Alzheimer's disease; *APOE* = apolipoprotein E; CSF = cerebral spinal fluid; NIA/AA = National Institute on Aging/Alzheimer's Association; PET = positron emission tomography.

Appendix 2
National Institute on Aging/Alzheimer's Association Criteria for Mild Alzheimer's Disease (cont.)

NIA/AA Category	Description
Probable AD dementia with increased level of certainty	**Probable AD dementia with documented decline** In persons who meet the core clinical criteria for probable AD dementia, documented cognitive decline increases the certainty that the condition represents an active, evolving pathologic process, but it does not specifically increase the certainty that the process is that of AD pathophysiology. Probable AD dementia with documented decline is defined as follows: evidence of progressive cognitive decline on subsequent evaluations based on information from informants and cognitive testing in the context of either formal neuropsychological evaluation or standardized mental status examinations. **Probable AD dementia in a carrier of a causative AD genetic mutation** In persons who meet the core clinical criteria for probable AD dementia, evidence of a causative genetic mutation (in APP, PSEN1, or PSEN2) increases the certainty that the condition is caused by AD pathology. The working group noted that carriage of the ε4 allele of the *APOE* gene was not sufficiently specific to be considered in this category.
Probable AD dementia with evidence of the AD pathophysiological process	AD dementia is part of a continuum of clinical and biological phenomena. AD dementia is fundamentally a clinical diagnosis. To make a diagnosis of AD dementia with biomarker support, the core clinical diagnosis of AD dementia must first be satisfied. Relevant biomarkers include amyloid-β (CSF or PET) and tau (CSF or PET).

AD = Alzheimer's disease; *APOE* = apolipoprotein E; CSF = cerebral spinal fluid; NIA/AA = National Institute on Aging/Alzheimer's Association; PET = positron emission tomography.

REFERENCES

McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:263–9.

Appendix 3
National Institute on Aging/Alzheimer's Association Criteria for Prodromal Alzheimer's Disease (Mild Cognitive Impairment due to Alzheimer's Disease)

NIA/AA Category	Clinical and Cognitive Criteria
Clinical criteria	• Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time) • Objective evidence of impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains) • Preservation of independence in functional abilities • Not demented
Etiology of MCI consistent with AD pathophysiological process	• Rule out vascular, traumatic, medical causes of cognitive decline, when possible • Provide evidence of longitudinal decline in cognition, when feasible • Report history consistent with AD genetic factors, when relevant
Prodromal AD dementia with evidence of the AD pathophysiological process	Prodromal AD is part of a continuum of clinical and biological phenomena. Prodromal AD is fundamentally a clinical diagnosis. To make a diagnosis of prodromal AD with biomarker support, the core clinical diagnosis of prodromal AD must first be satisfied. Relevant biomarkers include amyloid-β (CSF or PET) and tau (CSF or PET).

AD = Alzheimer's disease; CSF = cerebral spinal fluid; MCI = mild cognitive impairment; NIA/AA = National Institute on Aging/Alzheimer's Association; PET = positron emission tomography.

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Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data

The population pharmacokinetic positron emission tomography (PK-PET) response analysis of the gantenerumab Phase III study WN25203 data and aducanumab Phase Ib PET study model was built using pooled information from the gantenerumab Phase III study WN25203 and the aducanumab Phase Ib PRIME study. Details about how this population analysis was conducted and evaluated are provided herein.

1. MATERIALS AND METHODS

1.1 MODELING HYPOTHESIS

Based on the high degree of similarity between gantenerumab and aducanumab, it was assumed that both compounds share the same PK properties in terms of disposition, metabolism, elimination, and the same relationship between in serum concentrations and reduction in standardized uptake value ratio (SUVr) amyloid PET.

It was also assumed that the SUVr data from aducanumab and gantenerumab could be pooled given that they were derived using the same whole cerebellum reference region and that the sensorimotor region used only in the composite SUVr of aducanumab was having little effect on the SUVr values.

1.2 PHARMACOKINETIC AND PHARMCODYNAMIC DATA

A PK-pharmacodynamic (PD) dataset for PET model was built using information from the Phase III gantenerumab study (WN25203) together with information from Phase Ib aducanumab trial (PRIME).

2.2.1 Gantenerumab PK and PET Data

2.2.1.1 PK Information

Each patient participating in Study WN25203 provided samples for measurement of their PK serum concentrations at the following scheduled timepoints: Weeks 1, 8, 20, 44, 53, 68, 100, and 101.

The PK data from Study WN25203 were analyzed using a population PK model that was previously developed on the basis of Phase I studies.

The Phase I PK database comprised data from 235 patients and healthy volunteers for a total of 4082 PK observations. It contained data from both IV and SC administration, single and multiple repeated doses administered every 4 weeks (Q4W), with dose values ranging for the repeated dose administrations from 6 mg to 200 mg for the IV, 105 and 225 mg for the SC, and up to 300 mg SC and 400 mg IV when administered once. A two-compartment model with a 0 order followed

by first-order absorption best described the Phase I data. Population parameter values are reported in Table 1.

Table 1 Population PK Parameters Estimated from Phase I Study Data

Parameter	Mean	RSE%	BSV%	RSE%
CL (L/day)	0.336	3.20%	26.1%	6.9%
V2 (L)	3.52	5.60%	31.3%	18.5%
Q (L/day)	0.869	9.50%	55.5%	10.6%
V3 (L)	6.38	4.10%	24.9%	10%
KA (/day)	0.22	8.90%	52.2%	21.1%
D1 (/day)	0.0821	7.10%	96.6%	8.9%
F1 (–)	0.494	3.90%	42.8%	10.5%
PROP.ERR	0.196	5.40%		
ADD.ERR (μg/mL)	0.0121	21.70%		

ADD_ERR = additional error; CL=clearance; D1 = zero order rate constant; F1 = absolute bioavailability; KA = absorption rate constant; KeO = rate constant for drug transfer from serum to effect compartment; PK = pharmacokinetic; POW = power; PROP_ERR = proportional error; Q = intercompartmental clearance; RSE = relative standard error; SLOP = slope; V2 = central compartment; V3 = peripheral volume 3.

The population PK model was used to perform an empirical Bayesian analysis in non-linear mixed-effects model (NONMEM) of the PK data collected from Study WN25203 and to derive for each patient the individual PK parameters, as well as an estimation of the individual average concentrations over the period of observation.

2.2.1.2 PET Information

Among the 799 patients enrolled in Study WN25203, 114 patients participated in the amyloid PET substudy (using the AV-45 ligand). Scans were performed at baseline, Weeks 20, 60, and 100. For patients entering the 2-year, double-blinded portion of the trial (Part 2), another scan was obtained at Week 156.

PET data up to Week 100 (inclusive) were considered for the PK-PD modeling investigations, and the PET database comprised a total of 348 SUVr observations determined using the whole cerebellum as the reference region.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

2.2.2 Aducanumab PK and PET PD Data

Aducanumab PK and PET data were extracted from a poster (n°ADPD5–2113) and from slides that were presented at the 12th International Congress on Alzheimer's Disease and Parkinson's Disease (ADPD) in March 2015 in Nice, France.

The aducanumab data were collected in the Phase Ib, randomized, double-blind, placebo-controlled study (PRIME) in patients with prodromal or mild Alzheimer's disease. The study design involved a parallel-group design, with a 54-week treatment period. Patients received 14 IV infusions of aducanumab Q4W; four dose groups were evaluated, including the placebo group, and included the 1-mg/kg, 3-mg/kg, 6-mg/kg, and 10-mg/kg dose groups, respectively. SUVr measurements were performed at baseline, Week 26, and Week 54 and were determined using the whole cerebellum as the reference region.

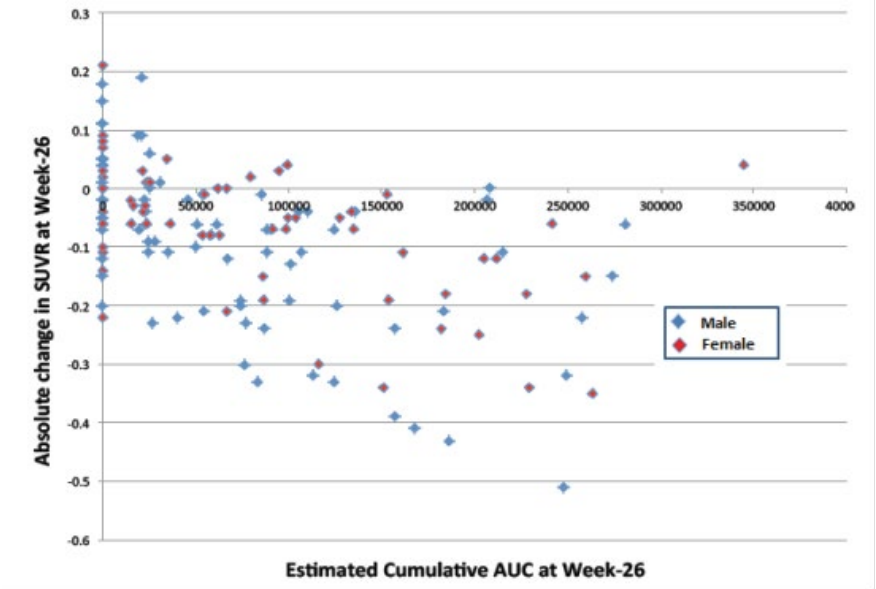
The following figures were used from the aducanumab poster and slides:

- A figure displaying the individual absolute change in SUVr at Week 26 in function of the individual cumulative area under the concentration-time curve (AUC) at Week 26 (see Figure 1)
- A table presenting the time course of the mean SUVr up to Week 54 by dose group (see Table 2)
- A figure displaying the relationship between the individual cumulative AUC at Week 26 and the four doses investigated in the PRIME study (see Figure 2)

The individual data, as depicted in Figure 1, were extracted and a database of 123 patients with their respective cumulative AUC values at Week 26 and the absolute change from baseline in SUVr. The mean data from Figure 2 were used to extrapolate the individual aducanumab PET data at Weeks 26 to 54 and, also, to assign a mean SUVr baseline value to each aducanumab dose group. In addition, the data from Figure 2 were used to determine from which dose group the individual cumulative AUC values at Week 26 from Figure 1 were most likely derived.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

Figure 1 Individual Absolute Change in SUVr Observed in Aducanumab Data at Week 26 with Respect to Cumulative Exposure



AUC = area under the concentration–time curve; SUVr = standardized uptake value ratio.
Source: Hang et al. 2015.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

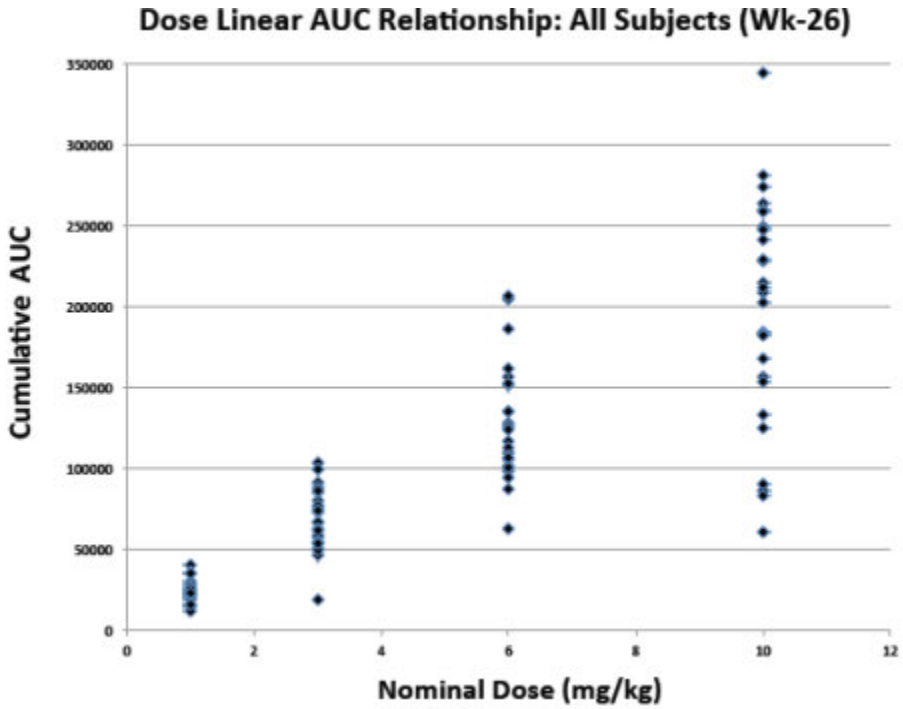
Table 2 Mean Composite PET SUVr Data Observed in the Aducanumab Phase Ib Trial (PRIME) per Dose Group, Using the Whole Cerebellum as Reference Region

	Observed Mean Composite SUVr		
Dose Group	Baseline	Week 26	Week 54
Placebo	1.45	1.42	1.42
1 mg/kg	1.45	1.395	1.346
3 mg/kg	1.471	1.365	1.3
6 mg/kg	1.44	1.288	–
10 mg/kg	1.434	1.223	1.152

SUVr = standardized uptake value ratio.

Source: Data derived from presented slide at ADPD conference.

Figure 2 Individual Dose–Exposure Relationship Observed in the Aducanumab Phase Ib Trial (PRIME)



AUC = area under the concentration–time curve.

Note: Subjects demonstrating low cumulative aducumab exposures were primarily due to missed doses.

Source: Hang et al. 2015.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

2.3 POPULATION PK-PD METHODS

2.3.1 Structural PK-PD Model

Several structural PK-PD models were evaluated to best describe the link between exposure and SUVr PET. The tested models included a direct relationship, as well as an indirect relationship, using an effect-compartment model to take into account a time delay for the concentrations in serum to reach the effect site.

Furthermore, several types of drug effect were tested, including a linear model, a power model, an E_{max} model, and a sigmoid E_{max} model.

No placebo models were evaluated because no specific placebo response was noticed during the observations period.

An additive error model was used for the residual variability. The baseline PET SUVr values were used as covariate in the model, but with an associated residual error of the same magnitude of the additive error model.

Inter-individual variability was tested on the PK-PD parameters by assuming a log-normal distribution.

2.3.2 PK-PD Model Selection and Evaluation

Models were selected by means of visual inspection of basic goodness-of-fits plots, including, but not limited to, plots of the observed data versus population (PRED) and individual predictions (IPRED), plots of individual weighted residuals (IWRES) versus IPRED, and the distribution of weighted residuals (WRES) over time. Relative standard errors (RSE) of the parameters were also compared to measure parameter precision. The NONMEM objective function value (OFV) was used to discriminate between nested models. This discrimination was based on a significance level of 0.05, which corresponds to a decrease of >3.84 in OFV (for one degree of freedom), as the difference in OFV is approximately χ^2 distributed.

Additionally, visual predictive check (VPC) was performed to test the model appropriateness by means of computing confidence intervals (CIs) derived from 1000 simulated data sets, using the final model and final parameter estimates, for each statistic (i.e., the median, the 5th and the 95th percentiles). Several VPCs were performed, either to test the appropriateness of the model when predicting the gantenerumab and aducanumab pooled dataset or to focus separately on the two compounds datasets. Furthermore, they were produced per level of exposure as well as per level of doses.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

2.3.3 Computer Programs

The analyses were performed in NONMEM Version 7.2, using FOCE INTERACTION (Beal and Sheiner 1992). Graphics and NONMEM datasets were created using Version 3.1.2 and/or the SAS system for Windows, Version 9.3.

2.4 COVARIATE ANALYSIS

Only limited covariate information was available from the aducanumab data, and an exploratory graphical analysis of individual post-hoc parameters was conducted only for the following covariates: PET baseline values, compound type, sex, and dose.

3. RESULTS

3.1 DATA

The final PK-PD dataset combining aducanumab and gantenerumab data included 237 patients with a total of 693 PET SUVr observations.

3.2 POPULATION EXPOSURE SUVr PET MODEL

The relationship between exposure and the PET SUVr reduction time course was best described by using a power model combined with an effect compartment to account for the delay between exposure and PET response. The model equations are as follows:

$$\mathrm{PET}(\mathrm{time}) = \mathrm{Base} * \left(1 - \mathrm{SLOP} * (\mathrm{Conc_E}(\mathrm{time}))^{\mathrm{POW}}\right)$$

with $$\frac{\mathrm{dConc_E}(\mathrm{time})}{\mathrm{dtime}} = \mathrm{Ke0} * (\mathrm{Conc}(\mathrm{time}) - \mathrm{Conc_E}(\mathrm{time}))$$

with Base the individual PET SUVr baseline value, $\mathrm{Conc_E}$ the predicted concentration at effect site, Conc the predicted concentration in serum, $\mathrm{Ke0}$ the rate constant for drug transfer from serum to effect compartment, and SLOP and POW the parameters driving the drug effect.

Parameter values are reported in Table 3.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

Table 3 Estimated Population PK-PD Parameters

Parameter	Mean (RSE%)	Value Inter-Individual Variability (RSE%)
Ke0 (Day $^{-1}$)	1.74×10^{-3} (38%)	127.3% (14%)
Equilibration half-life (weeks)	57	
SLOP	0.019 (33%)	—
POW (–)	0.716 (11%)	—
ADD_ERR	0.0659 (5%)	

ADD_ERR = additional error; KeO = rate constant for drug transfer from serum to the effect compartment; PD = pharmacodynamic; PK = pharmacokinetic; POW = power; RSE = relative standard error; SLOP = slope.

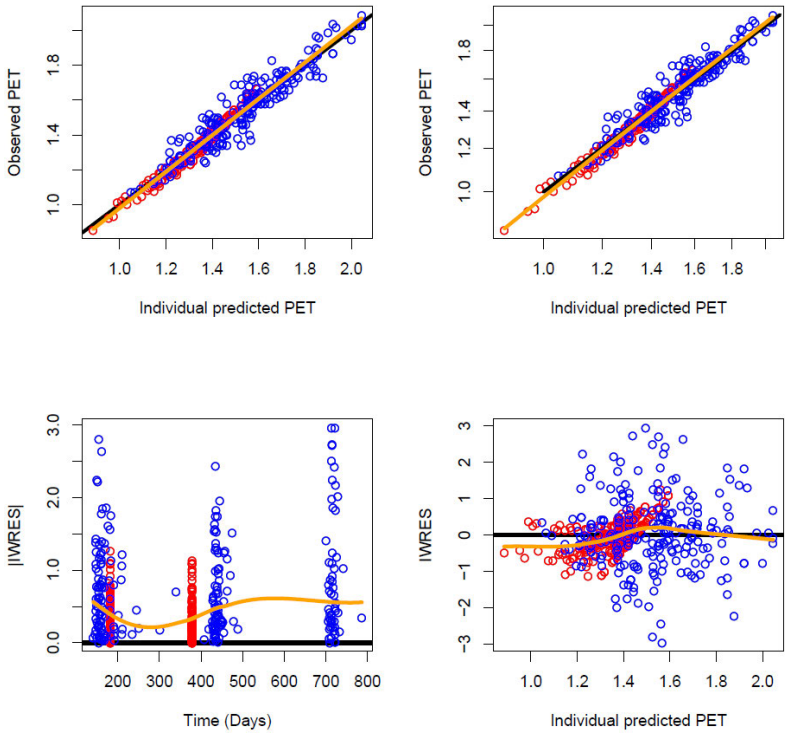
Inspection of the goodness-of-fit plots reported in Figure 3 shows that the final PK-PD model describes the data adequately without obvious bias in the population or individual predicted PET values. The VPCs are shown in Figures 5–7. The shaded areas indicate the 90% CIs (i.e., 5th and 95th percentiles) computed from simulations. The median and the 5th and 95th percentiles of the observed PK profiles are contained in their respective CIs, indicating that the final PK-PD model captures both the central tendency and the between-subject variability of both gantenerumab and aducanumab pharmacodynamics in the target populations of patients with prodromal and mild Alzheimer's disease.

3.3 COVARIATE ANALYSIS

The exploratory graphical covariate analysis is reported on Figure 4. Although a small trend between PET baseline values and estimated individual Ke0, this graphical analysis did not reveal any relevant covariate relationships that would require further investigation.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

Figure 3 Goodness-of-Fit Plots for the Final PK-PD Model

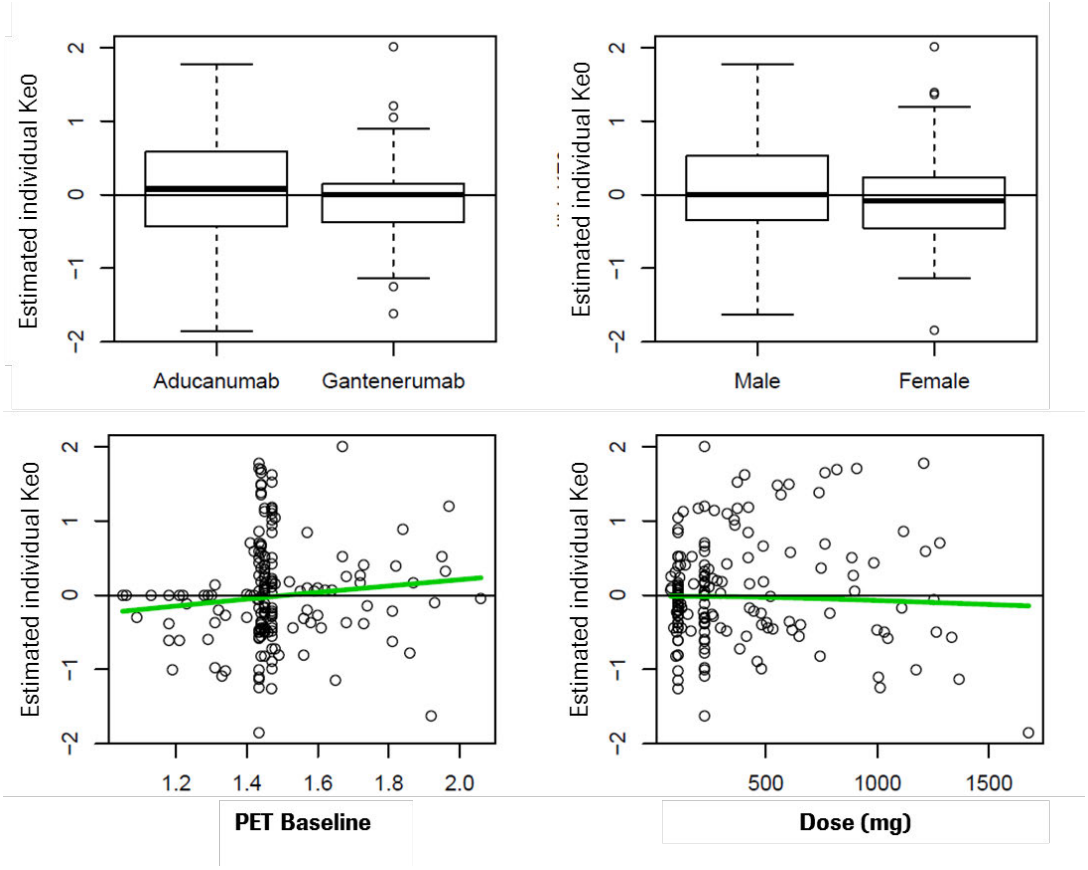


IWES = individual weighted residual value; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

Note: The red dots represent the aducanumab compound, and blue dots represent gantenerumab compound. The orange lines correspond to a smoothing of the data.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

Figure 4 Exploratory Analysis of Covariates (by Compound Type, Sex, PET Baseline Value, and Dose [in milligrams] Value with Respect to Estimated Individual Ke0)

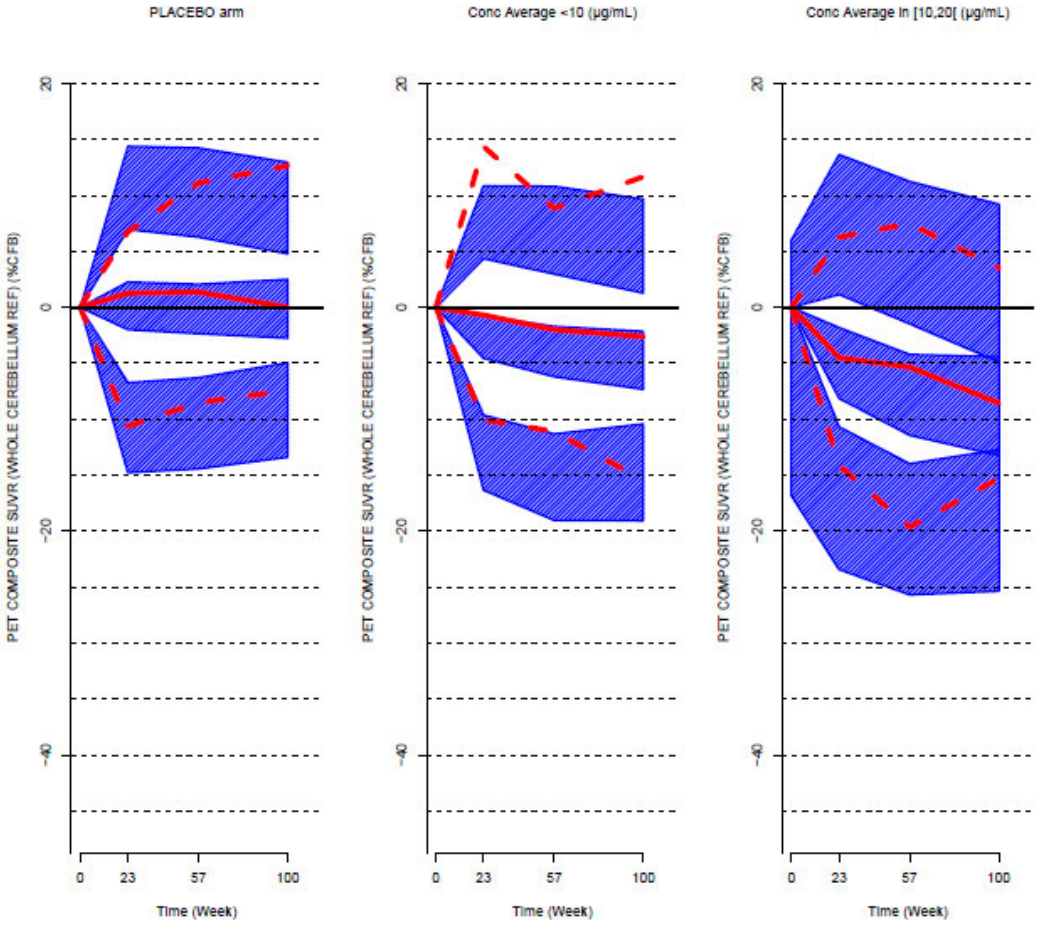


KeO = rate constant for drug transfer from serum to the effect compartment; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

Note: Dose was investigated in milligrams, using a mean weight of 70 kg for doses the aducanumab PRIME study. The green line corresponds to a smoothing of the data.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

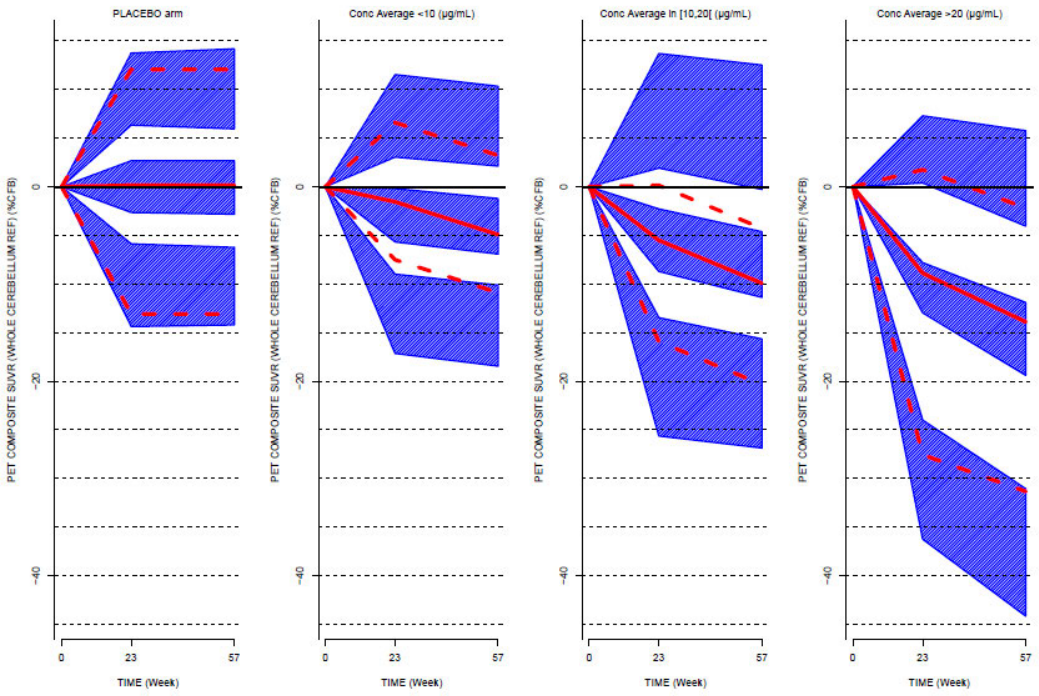
Figure 5 Visual Predictive Check of the PET Model by Category of Serum Concentration Exposure for the Gantenerumab WN25203 Alone



CFB = change from baseline; Conc = concentration; KeO = rate constant for drug transfer from serum to the effect compartment; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

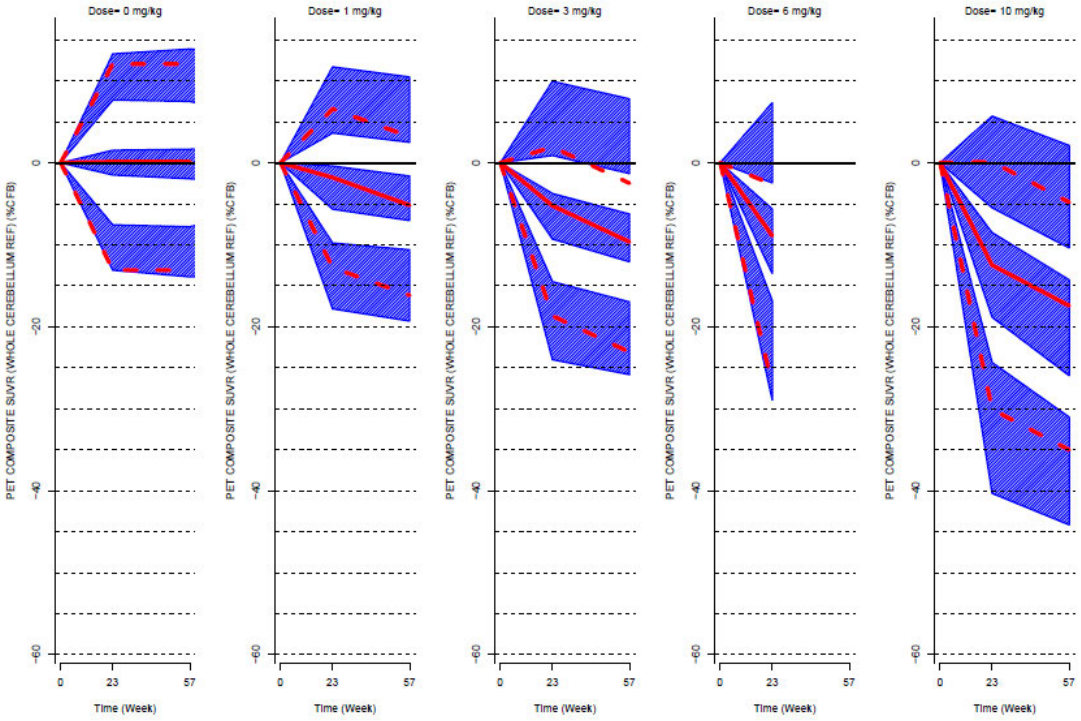
Figure 6 Visual Predictive Check of the PET Model Per Category of Serum Concentration Exposure for the Aducanumab PRIME Study Alone



KeO = rate constant for drug transfer from serum to the effect compartment; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

Figure 7 Visual Predictive Check of the PET Model by Category of Expected Dose Group for the Aducanumab PRIME Trial Alone



KeO = rate constant for drug transfer from serum to the effect compartment; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data (cont.)

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Hang Y, Chiao P, Sevigny J, et al. Pharmacokinetic and pharmacodynamic (PK-PD) assessment and covariate analysis of aducanumab (BIIB037) in a randomized, double-blind, placebo-controlled, Phase 1b study (PRIME) in subjects with prodromal or mild Alzheimer's disease. 12th International Congress on Alzheimer's and Parkinson's Disease. Poster presentation. March 2015. Nice, France.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model

1. BACKGROUND

Hutmacher et al. (2013) presented a pharmacodynamic (PD) model for bapineuzumab addressing the first occurrence of amyloid-related imaging abnormalities, or ARIAs, of "vasogenic edema" (ARIA-E) events. Patients received constant dose regimens of 0.5, 1, and 2 mg/kg given every 13 weeks over 1.5 years. A total of 2435 patients with 243 ARIA-E events were analyzed. As shown below, a log hazard model was developed that included three elements:

- A baseline value (I_{BS}) reflecting a constant ARIA-E hazard for apolipoprotein E allele ε4 (*APOE* ε4) gene carriers and non-carriers, respectively
- Plasma drug concentrations (c) of bapineuzumab modulating the ARIA-E hazard through the maximum effect (E_{max}) of drug and 50% of the effective concentration (EC_{50}) parameters
- A time component continuously suppressing the ARIA-E hazard by the time (t) since first dosing. ET_{50} and γ modulated this effect.

$$\log h(t) = I_{BS} + \frac{E_{\max} \cdot c(t)}{c(t) + EC_{50}} \cdot \frac{ET_{50}^{\gamma}}{ET_{50}^{\gamma} + t^{\gamma}}$$

Because no model parameters were reported in Hutmacher et al. 2013, the parameters were derived from predicted time-concentration and time-hazard curves presented in Hutmacher et al. 2013 after digitizing the respective graphs for 0.5 mg/kg in *APOE ε4* carriers. I_{BS} parameters were obtained from the graphs directly, whereas the other parameters were calculated from the digitized data using MATLAB (or matrix laboratory) and maximum likelihood estimation. Parameter values are shown in Table 1.

Table 1 Estimated Pharmacodynamic Parameters for Bapineuzumab

I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (μg/mL)
8.7E-6 (non-carrier) 3.55E-5 (carrier)	323.441	2.146	6.891	2.64

2. ARIA EVENTS UNDER CONSTANT DOSING REGIMENS

The above model was applied to the double-blind phase of Study WN25203, in which patients received constant dose regimens of 105 and 225 mg of gantenerumab. Owing to paucity of ARIA event data and the assumed independence between time and study drug–related hazard model parameters, I_{BS}, ET_{50}, and γ were fixed to the bapineuzumab values, and only E_{max} and EC_{50} were estimated.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

The concentration-time course for gantenerumab in Study WN25203 was derived from a population pharmacokinetic (PK) model previously developed for Phase I studies. It covers both intravenous (IV) and subcutaneous (SC) administration, as well as single and multiple repeated doses every 4 weeks, with a range of dose values for the repeated dose administrations from 6 mg to 200 mg for IV administration, 105 mg and 225 mg for SC administration, and up to 300 mg SC and 400 mg for IV administration when given only once. The parameters for this model are presented in Table 2.

Table 2 Pharmacokinetic Parameters for Gantenerumab

CL (L/day)	Q (L/day)	V_2 (L)	V_3 (L)	k_a (1/d)	F1 (1/d)	D (1/d)
0.336	0.869	3.152	6.38	0.22	0.494	0.0821

An update of the population PK model parameters was not considered as newly available drug concentrations were within prediction ranges from the established PK model. The maximum likelihood estimation of the log hazard model parameters E_{max} and EC_{50} was performed using NONMEM software. ARIA-E events were interval censored with a cutoff at 742 days. A total of 797 patients with 50 ARIA-E events were analyzed.

Parameter estimates are shown in Table 3.

Table 3 ARIA-E Parameters for Gantenerumab

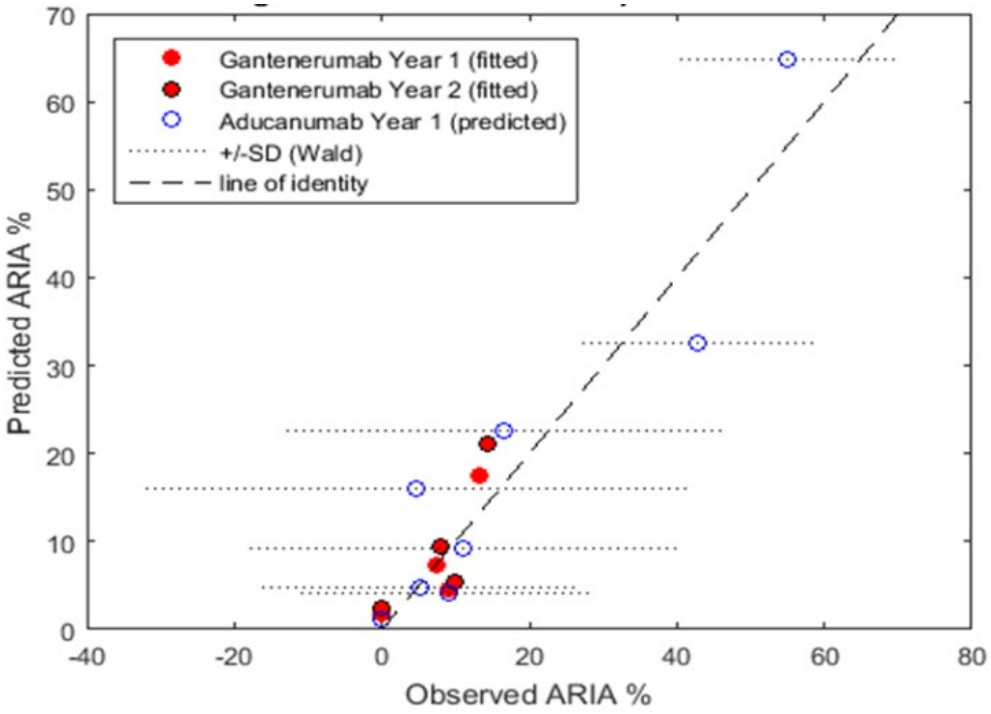
I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (μg/mL)
8.7E-6 (non-carrier) F 3.55E-5 (carrier) F	323.44 F	2.15 F	6.05±2.33	8.60±7.13

amyloid-related imaging abnormality–edema/effusion; F = fixed.

On inspection of the aducanumab PRIME study data (Sevigny et al. 2015), it became clear that the PK properties of gantenerumab and aducanumab are very similar. This supported an opportunity to test the hazard $PK\text{-}PD$ model applied to gantenerumab on IV aducanumab ARIA-E data. The ARIA–E model, which already provides a good description of the gantenerumab ARIA-E data in Study WN25203 after 1 and 2 years of treatment, respectively, also predicted the aducanumab Phase Ib ARIA-E data with a great degree of accuracy (see Figure 1), including the ARIA rate differences across *APOE* ε4 allele groups (see Figure 2), even though this approach is limited based on external aggregated data. This finding indicated that doses much larger than those

given in Study WN25203 can be described by the hazard model, provided that a constant dose regimen is used.

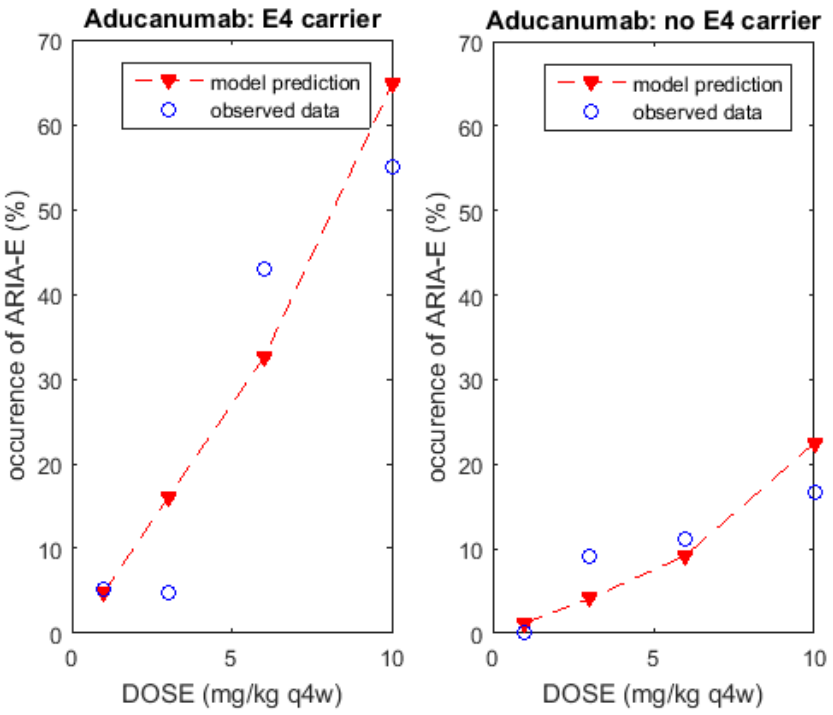
Figure 1 ARIA-E Prediction for IV Aducanumab Using Bapineuzumab Hazard Model Adapted to SC Gantenerumab



ARIA = amyloid-related imaging abnormality; ARIA-E = amyloid-related imaging abnormality–edema/effusion; IV = intravenous; SC = subcutaneous; SD = standard deviation.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Figure 2 Model-Based Predictions of ARIA-E Occurrence for Aducanumab by *APOE ε4* Carrier and Non-Carrier Status and Dose for a Q4W Dosing Regimen: Comparison to Observed Data in the PRIME Study



APOE ε4= apolipoprotein E, allele ε4; ARIA = amyloid-related imaging abnormality; ARIA-E = amyloid-related imaging abnormality–edema/effusion; IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous.

3. ARIA EVENTS UNDER DOSE TITRATION REGIMENS

3.1 MODELING DATABASE AS OF 6 DECEMBER 2016

To check the validity of the model under titration conditions, two patient groups were selected from the open-label extension studies of WN25203 and WN28745. The first group comprised 71 patients who received increasing doses of gantenerumab and received placebo during the double-blind phase of the study. The second group comprised 417 patients who received a constant dose of gantenerumab and who did not have treatment-free intervals of more than 70 days. The first group is representative for the intended Phase III design, and the second group was included to enhance the database and link the model to previously established results (see Table 4).

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Table 4 Patient Population Included in ARIA-E Model Building (Database as of 6 December 2016)

Number of Patients (Number of Events)	Study WN25203	Study WN28745	Total	Comment
Total included in study	**797 (63)**	**371 (35)**	**1168 (108)**	
Placebo treatment	236 (2)	111 (3)	347 (5)	Excluded from model building
Total included in study on active drug	**561 (61)**	**260 (32)**	**821 (103)**	
Total on active drug before OLE, or treatment gaps >70 days	125 (11)	108 (23)	333 (44)	Excluded from model building
Total included in model building	**436 (50)**	**52 (9)**	**488 (59)**	
Titrated without prior treatment	19 (1)	52 (9)	71 (10)	Included in model building
Constant dosing, and treatment gaps <70 days	417 (49)	—	417 (49)	Included in model building

ARIA-E = amyloid-related imaging abnormality–edema/effusion; OLE = open-label extension.

As noted previously, the maximum likelihood estimation was performed using NONMEM software. Estimated model parameters were E_{max} , EC_{50} and the baseline risk for carriers and non-carriers. ARIA-E events were observation interval censored.

Parameter estimates are shown in Table 5.

Table 5 ARIA-E Parameters for Gantenerumab When Applied to Titration Data

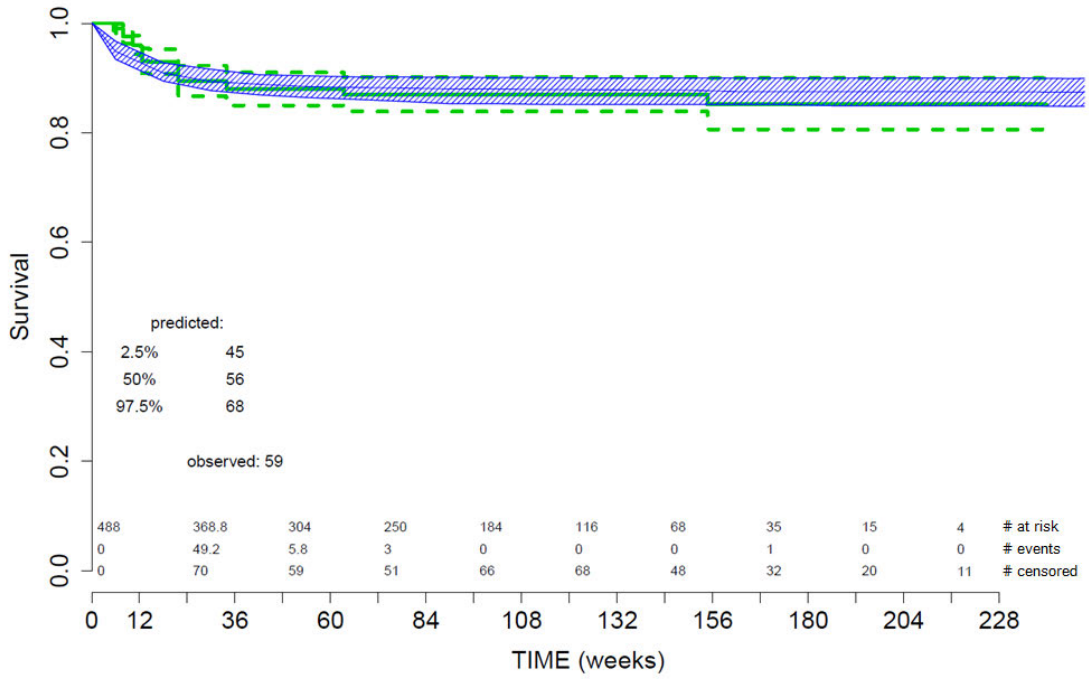
I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (μg/mL)
5.84 ± 4.22 E-6 (non-carrier) 11.9 ± 7.30 E-6 (carrier)	323.44 F	2.15 F	7.12 ± 1.03	5.16 ± 2.85

ARIA-E = amyloid-related imaging abnormality–edema/effusion; F = fixed.

Visual predictive checks were performed to assess model performance. As shown in Figure 3, the overall model performance was acceptable. Figure 4 presents a condition that was excluded from the model building. The apparent bias in the prediction might be attributable to a SCarlet RoAD study effect, which will be followed up during ongoing completion of the database.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Figure 3 Visual Predictive Check on Database Used for Model Building

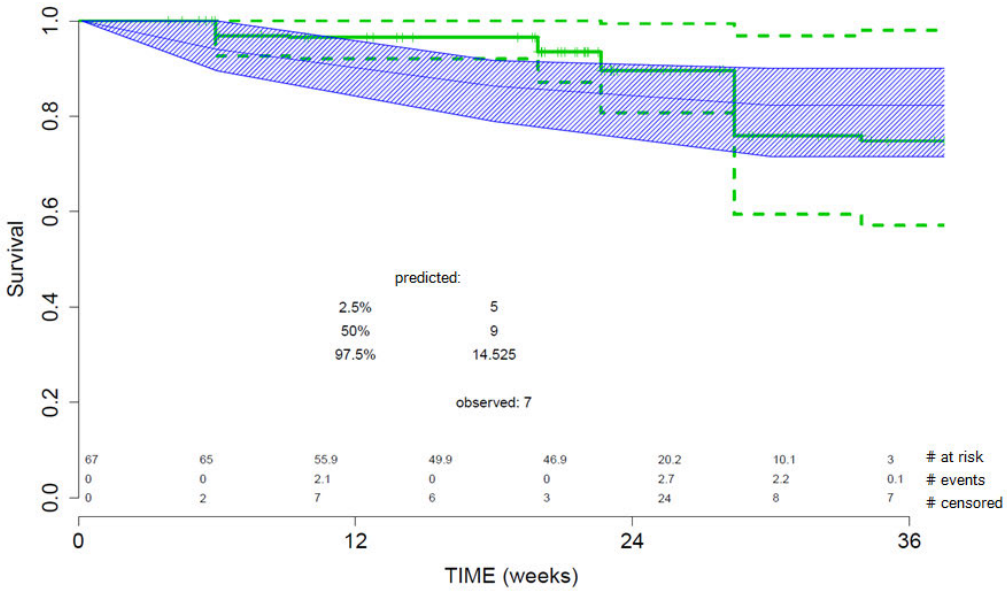


ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% [median], and 97.5%) and the actual observed number of events.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Figure 4 Visual Predictive Checks: Patients in SCarlet RoAD Study with Treatment Interruption >70 Days from Time 0 at Start of Open-Label Extension WN25203



ARIA-E = amyloid-related imaging abnormality–edema/effusion; OLE = open-label extension.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% [median], and 97.5%) and the actual observed number of events.

3.2 MODELING DATABASE AS OF 3 MARCH 2017

Table 6 presents an updated ARIA-E model building using data based on the cutoff date of 3 March 2017. In Table 7, ARIA-E parameters for gantenerumab are summarized when applied to titration data.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Table 6 Patient Population Included in ARIA-E Model Building (Database as of 3 March 2017)

Number of Patients (Number of Events)	Study WN25203	Study WN28745	Total	Comment
Total included in study	**797 (69)**	**371 (60)**	**1168 (129)**	
Placebo treatment	234 (2)	108 (3)	342 (5)	Excluded from model building
Database cleaning ongoing	3 (0)	—	3 (0)	Excluded from model building
Total included in study on active drug	**560 (67)**	**263 (57)**	**823 (124)**	
Long-term constant dose before titration	64 (9)	83 (17)	147 (26)	Excluded from model building
Total included into model building	**496 (58)**	**180 (40)**	**676 (98)**	
Titrated without prior treatment	24 (2)	67 [18]	91 (20)	Included in model building
Doses always smaller or equal to 225 mg	472 (56)	113 (22)	585 (78)	Included in model building

ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Table 7 ARIA-E Parameters for Gantenerumab when Applied to Titration Data

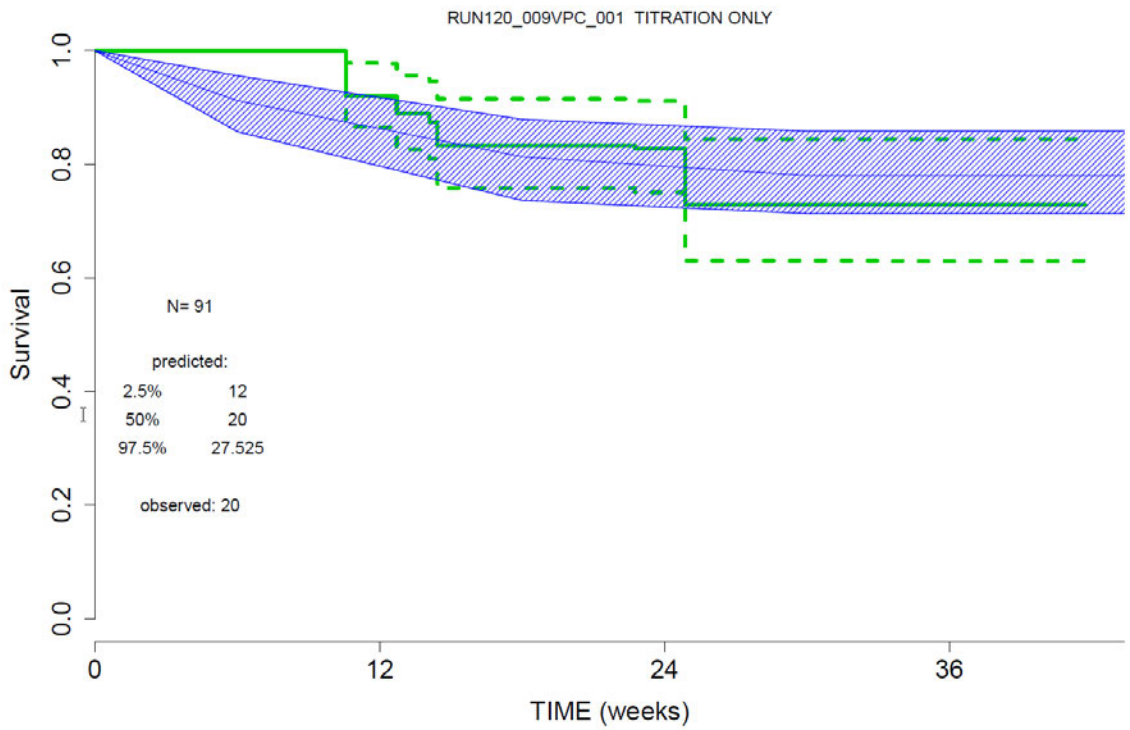
I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (µg/mL)
2.36 ± 1.01 E-5 (non-carrier) 3.75 ± 1.30 E-5 (carrier)	323.44 F	2.15 F	6.07 ± 0.702	7.75 ± 2.70

ARIA-E = amyloid-related imaging abnormality–edema/effusion; F = fixed.

Figures 5–7 show visual predictive checks for the final model. For both patients groups selected for model building, the diagnostics look acceptable (see Figures 5 and 6). For the excluded patient group who exhibited constant gantenerumab dosing followed by titration, often with 1 to 2 years of treatment gap in between, the diagnostics indicate a considerable mismatch. This could not be corrected by introducing covariates (such maximum treatment gap) into the model. It appears that the hazard model with its time component is not flexible enough for such regimens.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Figure 5 Visual Predictive Check on Titration Data Used for Model Building

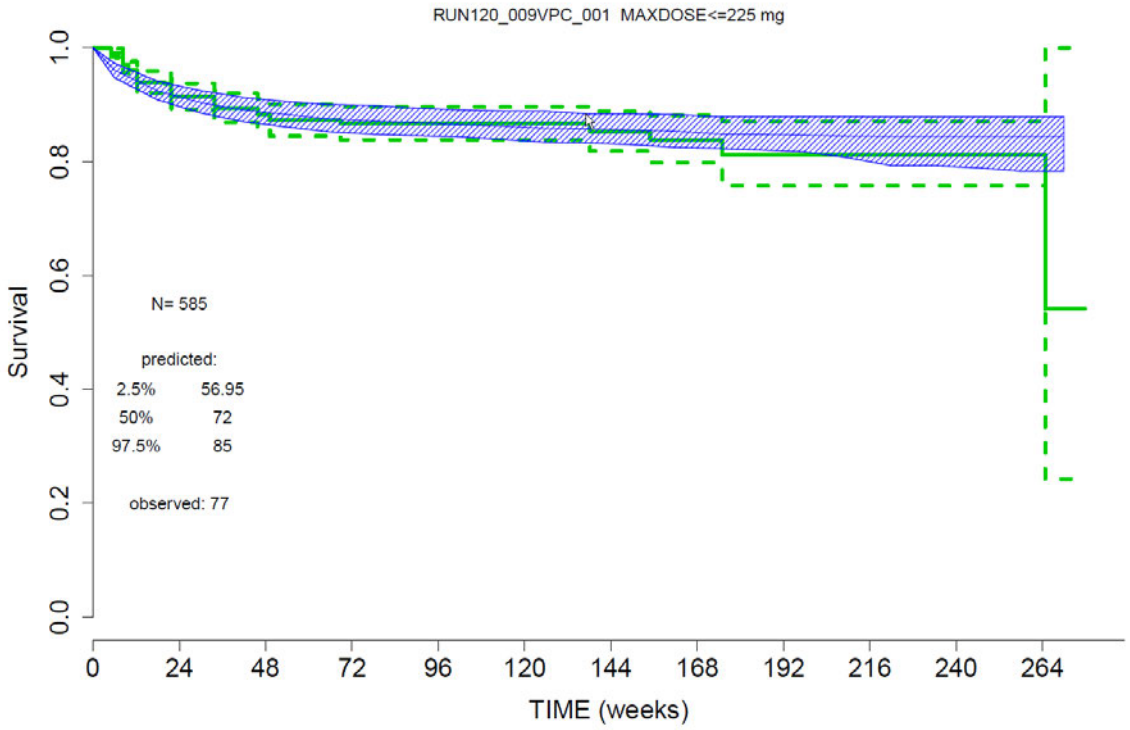


ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events (2.5%, 50% [median], and 97.5% percentiles), and the actual observed number of events. The apparent mismatch over the first 12 weeks is because no scan was performed during this period. Survival refers to the ARIA-E event-free proportion.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Figure 6 Visual Predictive Check on Data Used for Model Building (Based on Data from Patients Enrolled in the Double-Blind WN25203 and WN28745 Studies and Dosed with 225 mg)

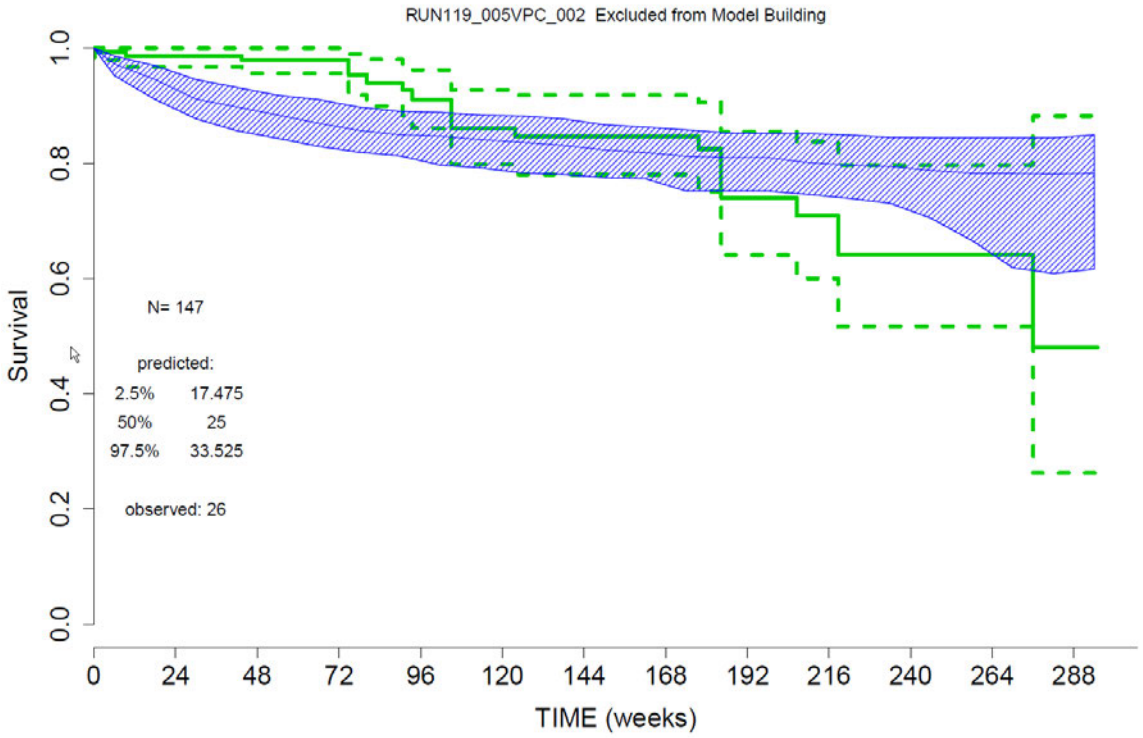


ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% (median), and 97.5%) and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Figure 7 Visual Predictive Check on Excluded Data from Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% (median), and 97.5%) and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

3.3. MODELING DATABASE AS OF 8 JULY 2017

Table 8 presents an updated ARIA-E model building using data based on the cutoff date of 8 July 2017. In Table 9, ARIA-E parameters for gantenerumab are summarized when applied to titration data.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Table 8 Patient Population Included in ARIA-E Model Building (Database as of 7 July 2017)

Number of Patients (Number of Events)	*Study WN25203*	*Study WN28745*	*Total*	*Comment*
Total included in study	***797 (75)***	***371 (60)***	***1168 (135)***	
Placebo treatment	*227 (2)*	*108 (3)*	*335 (5)*	*Excluded from model building*
Database cleaning ongoing	*2 (0)*	—	*2 (0)*	*Excluded from model building*
Total included in study on active drug	***568 (73)***	***263 (57)***	***831 (130)***	
Long-term constant dose before titration	*66 (14)*	*80 (16)*	*146 (30)*	*Excluded from model building*
Total included into model building	***502 (59)***	***183 (41)***	***685 (100)***	
Titrated without prior treatment	*36 (3)*	*70 (19)*	*106 (22)*	*Included in model building*
Doses always smaller or equal to 225 mg	*466 (56)*	*113 (22)*	*579 (78)*	*Included in model building*

ARIA-E =amyloid-related imaging abnormality–edema/effusion.

Table 9 ARIA-E Parameters for Gantenerumab when Applied to Titration Data

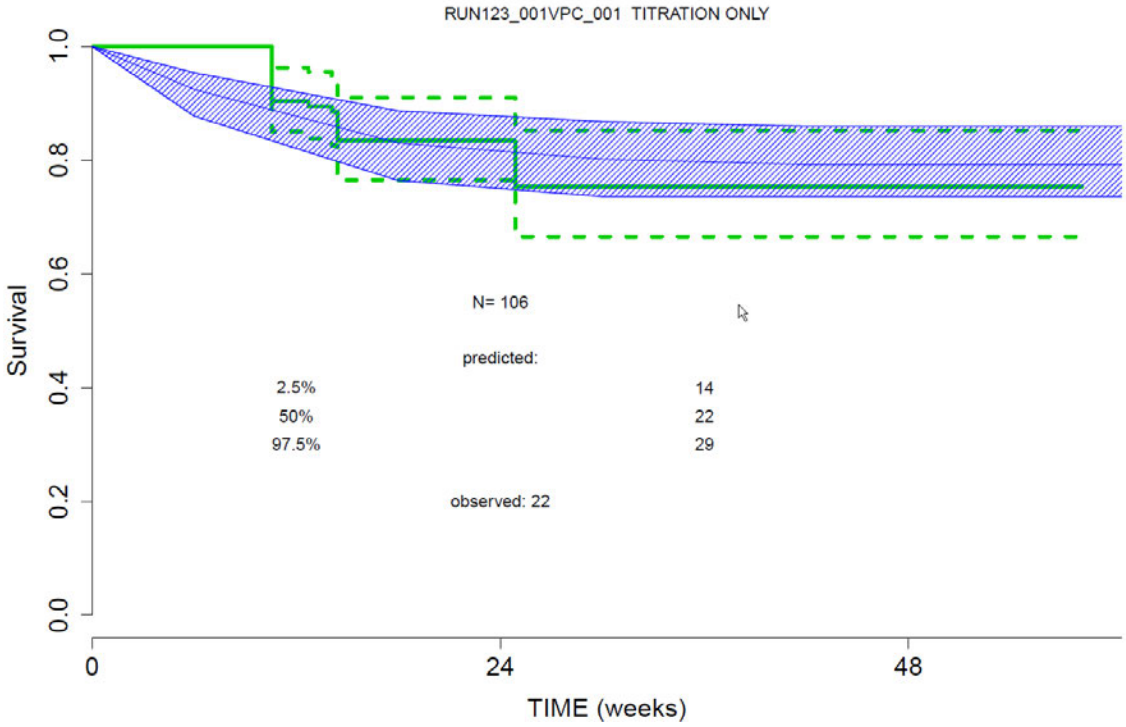
I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (µg/mL)
2.14 ±0.9742 E-5 (non-carrier) 3.52 ±1.24 E-5 (carrier)	323.44 F	2.15 F	5.92 ±0.688	6.78 ±2.88

ARIA-E =amyloid-related imaging abnormality–edema/effusion; F =fixed.

Figures 8–10 show visual predictive checks for the final model. For both patients groups selected for model building, the diagnostics look acceptable (see Figures 8 and 9). For the excluded patient group who exhibited constant gantenerumab dosing followed by titration, often with 1 to 2 years of treatment gap in between, the diagnostics indicate a considerable mismatch. This could not be corrected by introducing covariates (such maximum treatment gap) into the model. It appears that the hazard model with its time component is not flexible enough for such regimens.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Figure 8 Visual Predictive Check on Titration Data Used for Model Building

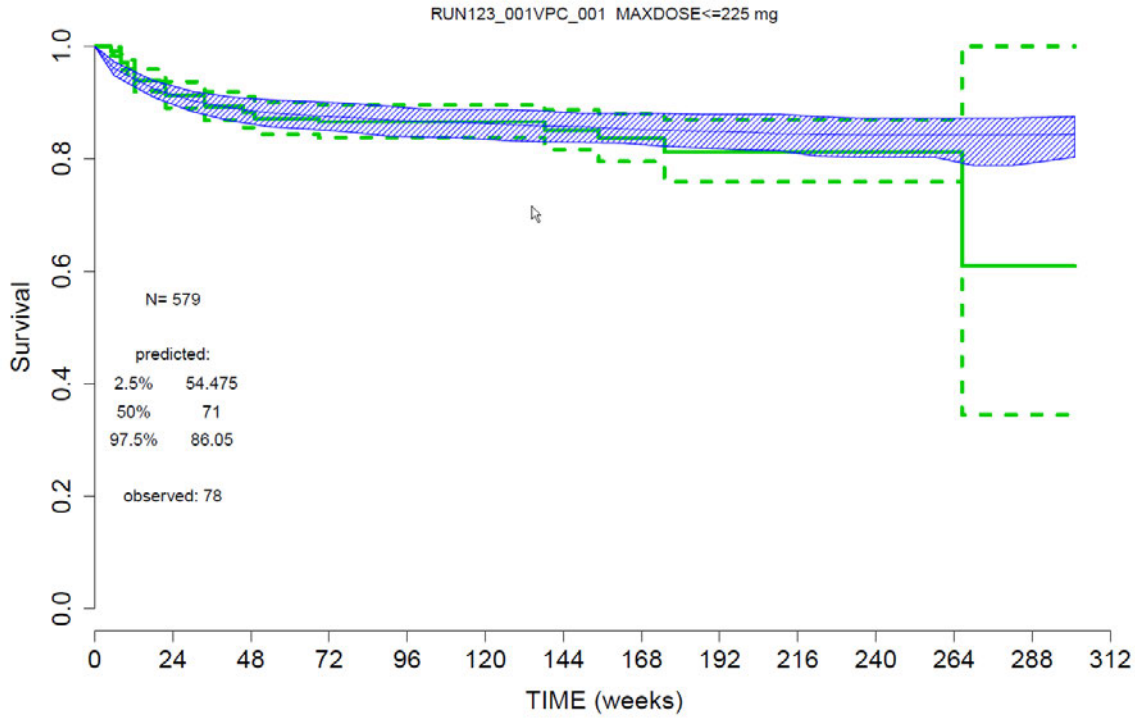


ARIA-E =amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events (2.5%, 50% [median], and 97.5% percentiles), and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Figure 9 Visual Predictive Check on Data Used for Model Building

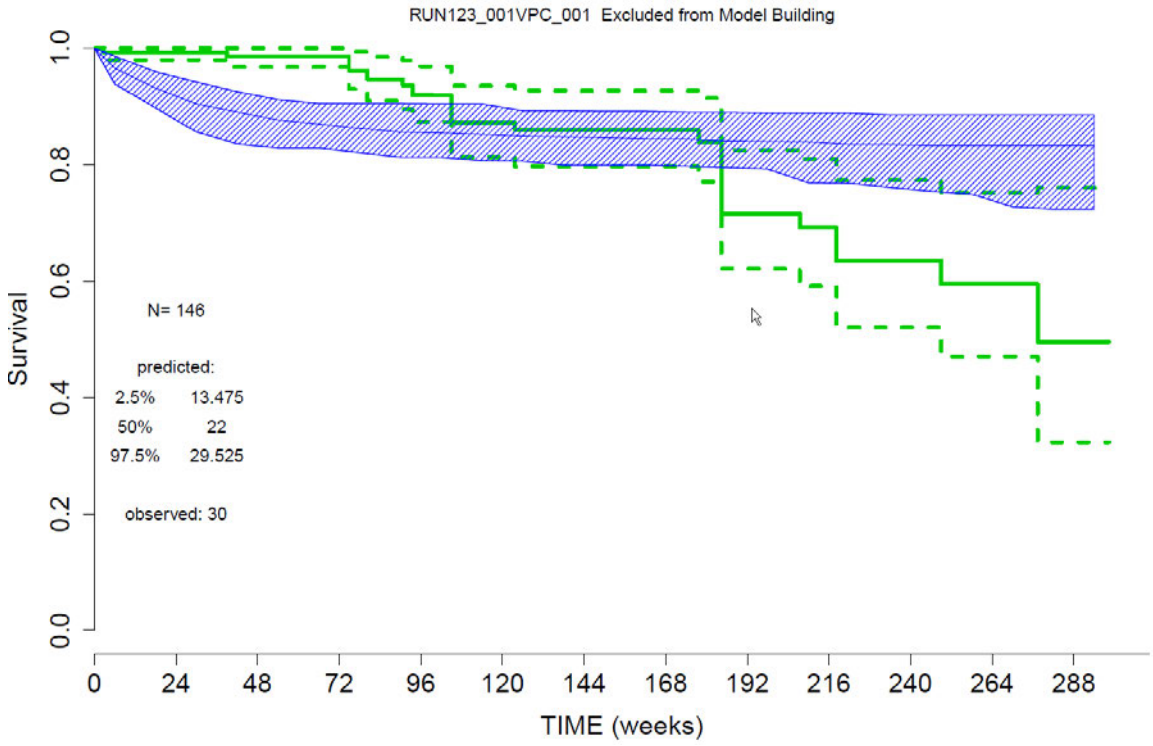


ARIA-E =amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% (median), and 97.5%) and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Figure 10 Visual Predictive Check on Excluded Data from Model Building



ARIA-E =amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% (median), and 97.5%) and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

REFERENCES

Hutmacher M, Hu C, Guenzler-Pukall V, et al. Pharmacokinetic-pharmacodynamic modeling of amyloid-related imaging abnormalities of edema following administration of bapineuzumab to subjects with mild to moderate Alzheimer's disease [poster]. Presented at the American Conference on Pharmacometrics 2013.

Sevigny J, Chiao P, Williams L, et al. Randomized, double-blind, Phase 1b study of BIIB037 in patients with prodromal or mild Alzheimer's disease. 12th International Congress on Alzheimer's and Parkinson's Disease. Symposium 26 March 2015. Nice, France.

Appendix 6
Management *Rules* for Amyloid-Related Imaging Abnormalities

Event	Characteristics	Action to Be Taken
ARIA-E	Asymptomatic ARIA-E and BGTS <4	Continue study drug at the same dose level (i.e., do not uptitrate) and repeat MRI scan 4 weeks later. – As long as BGTS is <4 and ≥1, continue study drug at the same dose level and repeat MRI 4 weeks later. – Once ARIA resolves, resume uptitration and obtain a MRI scan per the titration schedule. For patients randomized to the Q2W regimen, perform another MRI scan 3 months after study drug reintroduction.
	Symptomatic ARIA-E (of any size) or asymptomatic ARIA-E and BGTS ≥4	Temporarily interrupt study drug and perform MRI scans at 4-week intervals until symptoms and ARIA-E resolve. When symptoms and ARIA-E resolve, reintroduce study drug at dose given at the time the event was detected. – Perform a MRI scan before next scheduled dose for patients randomized to the Q4W regimen or after the second dose for patient randomized to the Q2W regimen. – If no new ARIA-E is detected, resume uptitration and obtain an MRI per titration schedule. For patients randomized to the Q2W regimen, perform another MRI scan 3 months after study drug reintroduction.
	Any recurrence of ARIA-E	Treat the same as the first event (based on symptoms and BGTS).
ARIA-H	>15 ARIA-H cumulatively (should not include any disseminated LH)	continue study drug.

ARIA-E = amyloid-related imaging abnormality–edema/effusion; ARIA-H=amyloid-related imaging abnormality–hemosiderin deposition; BGTS=Barkhof grand total score; LH=leptomeningeal hemosiderosis; MRI=magnetic resonance imaging; Q2W=every 2 weeks.

Appendix 7
Summary of Prohibited and Conditional Concomitant Medications

Drug Class [a]	*At Screening*	*During the Study*
Active immunization (i.e., vaccination) to prevent or postpone cognitive decline	***Prohibited*** *Any prior use*	***Prohibited*** *If initiated, patient must be discontinued from the study.*
Gantenerumab	***Prohibited*** *Any prior use*	***Prohibited*** *Outside of study settings*
Passive immunization therapies (i.e., monoclonal and/or polyclonal antibodies)	***Conditional*** *Prior use is allowed if medication was discontinued at least 12 months prior to screening.*	***Prohibited*** *If initiated, patient must be discontinued from the study.*
Experimental small molecules in treatment of Alzheimer's disease with putative effect on the progression of the disease (e.g., beta-secretase inhibitors)	***Conditional*** *Prior use is allowed if medication was discontinued more than 6 months or 5 half-lives (whichever is longer) prior to screening.*	***Prohibited*** *If initiated, patient must be discontinued from the study.*
Experimental drugs with putative symptomatic benefit in Alzheimer's disease (e.g., 5HT6 antagonists, muscarinic M1 positive allosteric modulators, histamine H3 antagonists)	***Conditional*** *Prior use is allowed if medication was discontinued more than 6 months or 5 half-lives (whichever is longer) prior to screening.*	***Prohibited*** *If initiated, patient must be discontinued from the study.*

[a] *The list is not exclusive. Examples of medications may vary based on local regulations and availability.*

[b] *If condition is not met, neuropsychological battery data for the next scheduled study visit may be censured.*

[c] *Low doses for non-cancerous conditions may be allowed on a case-by-case basis upon approval of the Medical Monitor.*

Appendix 7
Summary of Prohibited and Conditional Concomitant Medications (cont.)

Drug Class [a]	*At Screening*	*During the Study*
Experimental small molecules for any other indication	***Conditional*** *Prior use is allowed if medication was discontinued more than 4 months or 5 half-lives (whichever is longer) prior to screening.*	***Prohibited*** *If initiated, patient must be discontinued from the study.*
Cholinesterase inhibitors, N-methyl-D-aspartate receptor antagonists, and medical food supplements (where approved) for cognitive impairment or Alzheimer's disease (e.g., donepezil, galantamine, rivastigmine, memantine, Axona®, Souvenaid®)	***Conditional*** *If patient is on a stable dose for at least 3 months prior to screening and there is no plan to change the dose prior to completing the baseline visit*	***Conditional*** [b] *If chronic use is initiated, patient should be on stable dose for at least 3 months prior to the next scheduled neurocognitive assessment.*
Nootropics and stimulants (e.g., amphetamine, methylphenidate preparations, aniracetam, armodafinil, modafinil, piracetam)	***Conditional*** *Prior use is allowed if medication was discontinued more than 1 month or 5 half-lives (whichever is longer) prior to screening.*	***Prohibited*** *If initiated, patient may be discontinued from the study.*
Antiplatelet therapy (e.g., aspirin, clopidogrel, dipyridamol)	***Permitted***	***Permitted***
Opiates or opioid pain medications (e.g., oxycodone, hydrocodone, codeine, morphine, fentanyl, meperidine, methadone)	***Conditional*** *Prior use is allowed if medication was discontinued at least 3 months or 5 half-lives (whichever is longer) prior to screening.*	***Conditional*** [b] *Only allowed for intermittent short-term use and must be discontinued 2 days or at least 5 half-lives (whichever is longer) prior to any neurocognitive assessment.*

[a] *The list is not exclusive. Examples of medications may vary based on local regulations and availability.*

[b] *If condition is not met, neuropsychological battery data for the next scheduled study visit may be censured.*

[c] *Low doses for non-cancerous conditions may be allowed on a case-by-case basis upon approval of the Medical Monitor.*

Appendix 7
Summary of Prohibited and Conditional Concomitant Medications (cont.)

Drug Class [a]	*At Screening*	*During the Study*
Anticoagulants (e.g., heparin, warfarin, apixaban, rivaroxaban, dabigatran, edoxaban)	***Conditional*** *Prior use is allowed if medication was discontinued at least 3 months or 5 half-lives (whichever is longer) prior to screening.*	***Prohibited*** *If chronic use is initiated, patient must be discontinued from the study.* ***Note:*** *Short-term (e.g., perioperative) use of anticoagulant medications will not result in permanent discontinuation from the study; however, the plan for anticoagulation must be discussed with the Medical Monitor prior to initiating treatment.*
Selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, serotonin modulator and stimulator antidepressants (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram, duloxetine, desvenlafaxine, venlafaxine, agomelatine, vortioxetine)	***Conditional*** *If patient is on a stable dose for at least 3 months prior to screening and there is no plan to change the dose prior to completing the baseline visit*	***Conditional*** [b] *If chronic use is initiated, patient should be on stable dose for at least 3 months prior to the next scheduled neurocognitive assessment.*
Tricyclics and tetracyclics antidepressants (e.g., amitriptyline, nortriptyline, imipramine, desiramine, maprotiline, mirtazapine)	***Prohibited*** *Any prior use for treatment of depression, anxiety, insomnia* ***Conditional*** *Prior use for treatment of pain is allowed if medication was discontinued at least 12 months prior to screening.*	***Prohibited*** *If initiated, patient may be discontinued from the study.*

[a] *The list is not exclusive. Examples of medications may vary based on local regulations and availability.*

[b] *If condition is not met, neuropsychological battery data for the next scheduled study visit may be censured.*

[c] *Low doses for non-cancerous conditions may be allowed on a case-by-case basis upon approval of the Medical Monitor.*

Appendix 7
Summary of Prohibited and Conditional Concomitant Medications (cont.)

Drug Class [a]	*At Screening*	*During the Study*
Typical and atypical antipsychotic medication (e.g., aripiprazole, chlorpromazine, clozapine, fluphenazine, haloperidol, olanzapine, quetiapine, risperidone)	***Prohibited*** *Any prior chronic use* ***Conditional*** *If used as brief treatment for a non-psychiatric indication (e.g., emesis) and treatment was discontinued at least 6 months prior to screening*	***Conditional*** [b] *Only allowed for intermittent short-term use and must be discontinued 2 days or at least 5 half-lives (whichever is longer) prior to any neurocognitive assessment.*
Barbiturates, benzodiazepines, hypnotics (e.g., zopiclone, eszopiclone, zolpidem, flurazepam, ramelteon) and anticholinergic over-the-counter sleeping aids (e.g., diphenhydramine, doxylamine)	***Conditional*** *Prior chronic use is not permitted.* *Past episodic use is allowed, if treatment was completely discontinued at least 6 months prior to screening.*	***Conditional*** [b] *Short-term, episodic use is permitted except within 3 days or at least 5 half-lives (whichever is longer) of prior to any neurocognitive assessment.*
Over-the-counter first-generation antihistamines and anticholinergic sleeping aids (e.g., carbinoxamine, clemastine, chlorpheniramine, brompheniramine, diphenhydramine, doxylamine)	***Conditional*** *Prior chronic use is not permitted.* *Past episodic use is allowed, if treatment was completely discontinued at least 6 months prior to screening.*	***Conditional*** [b] *Short-term, episodic use is permitted except within 3 days or at least 5 half-lives (whichever is longer) of prior to any neurocognitive assessment.*
Anticonvulsants (e.g., phenytoin, carbamazepine, gabapentin, acetazolamide, acetazolam, clobazam, ethosuximide, levetiracetam, topiramate, vigabatrin)	***Prohibited*** *Any prior use for treatment of epilepsy/seizure disorders* ***Note:*** *Low-dose anticonvulsants for treatment of pain are allowed.*	***Prohibited*** *If initiated, patient may be discontinued from the study.* ***Note:*** *Low-dose anticonvulsants for treatment of pain are permitted.*

[a] *The list is not exclusive. Examples of medications may vary based on local regulations and availability.*

[b] *If condition is not met, neuropsychological battery data for the next scheduled study visit may be censured.*

[c] *Low doses for non-cancerous conditions may be allowed on a case-by-case basis upon approval of the Medical Monitor.*

Appendix 7
Summary of Prohibited and Conditional Concomitant Medications (cont.)

Drug Class [a]	*At Screening*	*During the Study*
L-Dopa/carbidopa, dopamine agonists, monoamine oxidase inhibitors or other medications for Parkinson disease, Parkinson disease dementia or dementia with Lewy bodies (e.g., deprenyl, apomorphine, benzhexol, orphenadrine, selegiline, ropinirole, pramipexole)	***Conditional*** *Prior use for treatment of Parkinson disease or other neurodegenerative conditions is only permitted if treatment was discontinued at least 12 months prior to screening.* ***Note:*** *Use of dopamine agonist for treatment for restless-leg syndrome is conditionally allowed, if patient is on a stable dose for at least 3 months prior to screening and there is no plan to change the dose prior to completing the baseline visit.*	***Prohibited*** *If initiated, patient may be discontinued from the study.*
Chemotherapy drugs [c]	***Prohibited*** *Within 24 months of screening*	***Prohibited*** *If initiated, patient may be discontinued from the study.*

[a] *The list is not exclusive. Examples of medications may vary based on local regulations and availability.*

[b] *If condition is not met, neuropsychological battery data for the next scheduled study visit may be censured.*

[c] *Low doses for non-cancerous conditions may be allowed on a case-by-case basis upon approval of the Medical Monitor.*

PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP EFFICACY AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN39658
VERSION NUMBER:	5
EUDRACT NUMBER:	2017-001365-24
IND NUMBER:	102,266
NCT NUMBER:	NCT03444870
TEST PRODUCT:	Gantenerumab (RO4909832)
MEDICAL MONITOR:	[redacted], *MBBS, PhD*
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
04-Aug-2021 07:47:21	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
4	*23 May 2020*
3	21 January 2020
2	11 February 2018
1	21 July 2017

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

The changes to the protocol, along with a rationale for each change, are summarized below:

- Section 1.3.5 Overall Benefit-Risk Summary has been updated to address the COVID-19 pandemic impact on the Benefit-Risk assessment for Study WN39658, as per the MHRA requirement
- Objectives and endpoints of the Double-Blind Treatment Period (Table 2) have been updated in the following manner:

– Corresponding endpoints for the 'exploratory efficacy' objective have been revised to remove 'in global outcome' as a criteria for the measurement of change from baseline to Week 116, which was added in error.

– The exploratory endpoint 'Time to clinically evident decline, defined as an increase of ≥ 2.0 in CDR-SOB subscore or ≥ 1 in at least four items of the FAQ' has been removed from Table 2, as it is not considered relevant anymore based on new available data.

– The exploratory endpoint 'Change from baseline to Week 116 measured by 'Function as assessed by the CDR function subscore" has been removed as it is no longer considered relevant based on new available data.

– The exploratory endpoint 'clinically evident decline as measured using the CDR' has been added to Table 2.

– The pharmacokinetic (PK) objective of the study has been changed to an exploratory PK objective to be consistent with the sparse PK sampling design and population modeling used to analyse the dose concentration–time data of gantenerumab. In addition, the protocol has been amended to enable early access PK, anti-drug antibodies (ADA) and pharmacodynamic (PD) biomarker samples. Early access will only be applied if there are sufficient sample data available to make an adequate assessment.

– The corresponding endpoints for the pharmacodynamic (PD) biomarker objective have been revised to clarify the duration of change as a measurement from baseline to Week 116 when assessing brain amyloid load, brain tau load and cerebral spinal fluid markers.

– The PD biomarker objective endpoint 'MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all participants ' has been reclassified as exploratory as it is no longer considered secondary based on new available data.

- Sections 3.1.1 and 4.1.3 have been updated to clarify that the open-label extension (OLE) of Study WN39658 is not applicable in countries that cannot run Study WN42171.
- Sections 4.1.2.7, 4.4.1, 4.7.2, and Appendix 1 have been revised to clarify the Medical Monitor's responsibility to review and support patient cohort management

and other protocol activities. Any reference to approval by the Medical Monitor with regards to medical decisions following enrollment has been removed from the protocol. The Principal Investigator (PI) may consult with the Medical Monitor/Sponsor for advice or clarification and may share risk factor information pertinent to the patient, but the medical decisions for the study participants are the responsibility of the PI.

- Section 4.1.3 has been amended to replace Week 104 with Week 116 (or Week 128, if applicable) which was omitted in the previous protocol amendment.
- Section 4.6.3 and 4.6.4 have been amended to better clarify the order of assessments during the study visits.
- Section 6.4.1 has been updated according to the estimand framework outlined in the ICH-E9 draft addendum with regards to the primary endpoint.
- Section 6.4.2 has been updated to remove the reference to time to event, which was included in error.
- Sections 6.4.4, 6.5 and 6.6 have been updated to clarify that a separate cut off may be necessary for PD biomarker, PK, and ADA samples to allow early access to PD biomarker samples and ensure expedient data analyses.
- Section 6.7.1 and 6.7.2 have been updated to include additional details surrounding the conduct of an interim analysis, should one be implemented.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP EFFICACY AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN39658
VERSION NUMBER:	5
EUDRACT NUMBER:	2017-001365-24
IND NUMBER:	102,266
NCT NUMBER:	NCT03444870
TEST PRODUCT:	Gantenerumab (RO4909832)
MEDICAL MONITOR:	[redacted], *MBBS, PhD*
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____

Principal Investigator's Signature Date

Please return the signed original of this form to the Sponsor or its designee. Please retain a signed copy of the form for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP EFFICACY AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN39658
VERSION NUMBER:	5
EUDRACT NUMBER:	2017-001365-24
IND NUMBER:	102,266
NCT NUMBER:	NCT03444870
TEST PRODUCT:	Gantenerumab (RO4909832)
PHASE:	Phase III
INDICATION:	Alzheimer's disease
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy and safety of gantenerumab compared with placebo in participants with early (prodromal to mild) Alzheimer's disease (AD). Specific objectives and corresponding endpoints for the study are outlined below for the double-blind treatment period and for the OLE period.

Objectives and Corresponding Endpoints for the Double-Blind Treatment Period

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of gantenerumab administered by SC injection compared with placebo	The change in global outcome from baseline (Day 1) to Week 116 [a], as measured by the CDR-SOB
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo on cognition and function	The change from baseline to Week 116 [a] in cognition and/or function, as measured by: • MMSE total score • ADAS-Cog11 and ADAS-Cog13 • Verbal Fluency Task • Coding • FAQ • ADCS-ADL total score and instrumental score
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo	The change from baseline to Week 116 [a] in the following: • Clinically evident decline *as measured using the CDR* • Severity, as assessed by the CDR Global Score • Dependence level, as derived from the ADCS-ADL score • Health-related quality of life, as assessed by the QoL-AD scale • Behavioral and neuropsychiatric symptoms of AD, as measured by the NPI-Q • Study partner burden, as assessed by the ZCI-AD scale • Elements of resource utilization, as assessed by the RUD-Lite • Health outcomes in participant and study partner, as measured by EQ-5D questionnaire

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

[a] If the double-blind treatment period is extended by a total of 24 weeks, the endpoints will be based on change from baseline to Week 128.

Objectives and Corresponding Endpoints for the Double-Blind Treatment Period (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of gantenerumab compared with placebo	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Presence of ADAs during the study relative to the presence of ADAs at baseline (in active treatment group only)
Pharmacodynamic Biomarker Objective	**Corresponding Endpoints**
To evaluate the effect of gantenerumab compared with placebo in participants with early (prodromal to mild) Alzheimer's disease	• Change from baseline *to Week 116* in brain amyloid load, as measured by amyloid PET scan in a subset of participants • Change from baseline *to Week 116* in brain tau load, as measured by tau PET scan in a subset of participants • Change from baseline *to Week 116* in cerebral spinal fluid markers of disease in a subset of participants, including, but not limited to, total tau, and phosphorylated tau
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo in participants with early (prodromal to mild) Alzheimer's disease	• Change over time in plasma *and other CSF* biomarkers • Change from baseline to Week 116 [a] in functional brain connectivity, as measured by resting-state functional MRI (where available) • Change from baseline to Week 116 [a] in integrity of white matter, as measured by DTI-MRI (where available) • *MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all participants*
Exploratory **Pharmacokinetic Objective**	**Corresponding Endpoints**
• To characterize the PK profile of gantenerumab	• Plasma concentration of gantenerumab (administered subcutaneously) at specified timepoints

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

[a] If the double-blind treatment period is extended by 24 weeks, the final endpoints will be based on change from baseline to Week 128.

Objectives and Corresponding Endpoints for the Open-Label Extension Period

Safety Objective	Corresponding Endpoints
• To evaluate the long-term safety and tolerability of SC gantenerumab in participants with early AD	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Presence of ADAs during the study relative to the presence of ADAs at baseline
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To assess the long-term efficacy of SC gantenerumab in participants with early AD	• The change in cognition, function and other outcomes over time, as measured by: • CDR • MMSE • ADAS-Cog11 and ADAS-Cog13 • Verbal Fluency Task • Coding • FAQ • ADCS-ADL • Health-related quality of life, as assessed by the QoL-AD scale • Behavioral and neuropsychiatric symptoms of AD, as measured by the NPI-Q • Study partner burden, as assessed by the ZCI-AD scale • Elements of resource utilization, as assessed by the RUD-Lite • Health outcomes in participant and study partner, as measured by EQ-5D questionnaire

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

Objectives and Corresponding Endpoints for the Open-Label Extension Period (cont.)

Exploratory Pharmacodynamic Biomarker Objective	Corresponding Endpoints
• To evaluate the long-term effect of SC gantenerumab in participants with early AD	• Brain amyloid load over time, as measured by amyloid PET scan in a subset of participants • Brain tau load over time, as measured by tau PET scan in a subset of participants • Cerebral spinal fluid markers of disease over time in a subset of participants, including, but not limited to, $A\beta_{1-42}$, total tau, and phosphorylated tau • MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, functional brain connectivity, integrity of white matter in all participants • Plasma markers over time *in all participants*

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

Study Design

Description of Study

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of gantenerumab in participants with early (prodromal to mild) AD.

The planned number of participants for the global enrollment phase for the study is approximately 1016 participants: randomized in a 1:1 ratio to receive gantenerumab and placebo (508 participants randomized to gantenerumab and 508 randomized to placebo). To maintain a balanced number of participants enrolled in each treatment arm and to ensure that the arms are comparable, randomization will be stratified by stage of disease (prodromal AD vs. mild AD), apolipoprotein E (*APOE)* allele status (presence vs. absence of the ε4 allele), use of AD medication (presence vs. absent), geographic region (Western Europe and Australia vs. Rest of the World vs. North America) and participation in longitudinal amyloid and tau positron emission tomography (PET) substudies. Approximately 175 centers in approximately 15 countries worldwide will participate in this study.

Participants will be selected on the basis of clinical diagnosis of probable AD (according to the National Institute on Aging/Alzheimer's Association [NIA/AA] diagnostic criteria and guidelines for AD) or prodromal AD (according to the NIA/AA diagnostic criteria and guidelines for mild cognitive impairment (MCI) due to AD). The aim of the study is to recruit approximately 50% of the participants with prodromal AD.

Eligible participants will be 50–90 years old, inclusive, must show evidence of β-amyloid pathology as indicated by the cerebral spinal fluid (CSF) tau to $A\beta_{42}$ ratio (CSF-enrolled participants) or positive amyloid PET scan by visual read (PET-enrolled participants), and meet eligibility criteria.

The study will consist of a screening period of up to 12 weeks in length following the signing of informed consent. Sites also have the option to prescreen participants on the Free and Cued Selective Reminding Test (FCSRT) and Mini-Mental State Examination (MMSE). Participants must sign a separate Informed Consent Form before administration of these tests if used for prescreening. If the results confirm a participant's eligibility, then the FCSRT and MMSE will not have to be completed again during the screening period as long as the test has been done within 12 weeks prior the baseline.

Eligible participants will then undergo baseline visit assessments (Day 1) prior to receiving the first dose of blinded study drug (gantenerumab or placebo). Participants will continue in the double-blind treatment period.

Due to the global impact of the COVID-19 pandemic and the resulting disruption in study drug administration, the duration of the double-blind treatment period will be extended by 12 weeks, with the possibility of an additional 12-week extension (for a total of 24 weeks). This may result in the following scenarios:

- Scenario 1: Participants who are enrolled and active in the double-blind treatment period after implementation of Protocol Version 4 will have the double-blind treatment period extended by 12 weeks, with the final efficacy and safety visit at Week 116.
- Scenario 2: If the COVID-19 pandemic results in greater than anticipated disruptions to study drug administration, then the Sponsor has the option to extend the double-blind treatment period by an additional 12 weeks, with the final efficacy and safety visit at Week 128. This extension will be mandatory for all patients who are active in the double-blind treatment period at the time that the extension decision is implemented.

Participants who have already had the last study drug administration at Week 102 and their final efficacy and safety visit at Week 104 and who have completed the double-blind treatment period prior to implementation of *the study extension by 12 weeks*, will continue into the OLE of either the WN39658 study or the WN42171 study. Alternatively, they will continue into the safety follow-up period.

For participants who enroll or who are active in the double-blind treatment period at the time of implementation of *the study extension by 12 weeks*, visits and study drug administration will occur Q4W until participants reach the target dose, which will be 510 mg Q2W. After the last dose of study drug (Week 114 for scenario 1 and Week 126 for scenario 2, if applicable), final efficacy and safety assessments will be performed 2 weeks later (at Week 116 for scenario 1 and at Week 128 for scenario 2, if applicable). Participants may then enroll in an OLE study if they are eligible (either in the OLE part of this study or in the WN42171 study) or have safety follow-up visits 14 and 50 weeks after the last dose for safety and limited efficacy assessments.

All participants who prematurely discontinue treatment will continue participating in the study and will be asked to return for collection of safety and limited efficacy data.

Participants will undergo brain magnetic resonance imaging (MRI) examinations for safety monitoring and longitudinal changes in brain structure. MRI scans will be read by a central MRI reader. Participants will also undergo standard tests to monitor safety (blood tests, ECG), as well as the Columbia–Suicide Severity Rating Scale (C-SSRS) to monitor for suicidality, tests for cognition, function, and quality-of-life (QoL) status. Blood samples for the assessment of PK samples, pharmacodynamic (PD) biomarkers, and *ADAs* will be obtained from all participants.

The incidence and nature of adverse events, serious adverse events, amyloid-related imaging abnormalities–edema/effusion (ARIA-E) and ARIA–hemosiderin deposition (ARIA-H), injection site reactions (ISRs), adverse events of special interest, ECGs, and laboratory abnormalities will be assessed on a regular basis by an unblinded independent Data Monitoring Committee (iDMC).

Once the double-blind treatment period is completed, participants who consent and are eligible may opt to participate in an OLE. If the stand-alone open-label study (Study WN42171) is not open for enrollment at the time that a participant completes the double-blind treatment period of this study, then the participant will use the OLE procedures described in this study. These participants will then transition to Study WN42171 after they have completed the entire schedule of activities in the OLE of this study and the protocol for Study WN42171 is available and approved as per local requirements. If Study WN42171 is open for enrollment at the time

that a participant completes the double-blind treatment period of this study, then the participant will enroll directly in Study WN42171 and not in the OLE portion of this protocol. *The OLE of Study WN39658 is not applicable in countries that cannot run Study WN42171.*

The study consists of three distinct periods:

- Screening (including an optional prescreening): The screening period may last up to 12 weeks for each eligible participant.
- Double-blind treatment period: After screening, participants who meet all eligibility criteria will be randomly assigned to one of two arms (gantenerumab or placebo) in a 1:1 ratio. Following baseline assessments, each participant will receive a minimum of nine SC Q4W administrations of study drug (uptitration period), followed by up to 40 administrations of study drug in the double-blind treatment period in scenario 1 or up to 46 administrations in scenario 2, if applicable. The last dose of study drug will be administered at Week 114 in scenario 1 and at Week 126 in scenario 2, if applicable. At the end of the double-blind treatment period, 2 weeks after the last dose, all participants will undergo the final safety and efficacy study visit. Participants who have already completed the double-blind treatment period prior to implementation of *the study extension by 12 weeks* will have received 34 SC Q2W administrations of study drug during the double-blind treatment period. The last dose will be administered at Week 102, and their final efficacy and safety visit will be at Week 104.
- Post–double-blind treatment period: After the final efficacy and safety study visit, all participants will be asked to come back for the long-term follow-up visits or to continue in the OLE.

  Long-term follow-up: Long-term follow-up will consist of a 50-week follow-up period with evaluations at Weeks 14 and 50 after completion of study drug administration. Participants who withdraw early during the double-blind treatment period or during the OLE period are also asked to complete the long-term follow-up visits.

  OLE: All eligible participants will have the opportunity to enter an OLE study.

  – Eligible participants who enrolled early in the WN39658 study may start the OLE and will then transition to the open-label study WN42171 (details will be provided in protocol WN42171). Participants who terminated the WN39658 OLE early will be asked to come back for long-term follow-up visits.
  – If the WN42171 protocol is available and approved by local authorities, the remaining eligible participants will directly be enrolled in the open-label study WN42171.

China Enrollment Plan

Based on historical data, participant recruitment is expected to take longer in China; therefore, a specific China enrollment plan has been established. Thus, if at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the National Medical Products Administration (NMPA) during the global enrollment phase, additional participants may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. All participants enrolled at NMPA-recognized sites in the global enrollment phase will be included in the primary analysis. All participants enrolled at NMPA-recognized sites in the global enrollment phase and the China extension phases will be included in a China-specific analysis. Details will be provided in the Statistical Analysis Plan (SAP).

Substudies

The substudies associated with Study WN39658 will be described in separate protocols, and participants consenting to enroll in these substudies will be asked to sign the associated Informed Consent Forms.

To date, there are two substudies associated with Study WN39658: a longitudinal Amyloid PET substudy and a longitudinal Tau PET substudy. The amyloid- and tau-PET assessments will allow a longitudinal evaluation of the effect of gantenerumab on brain amyloid deposition as measured by florbetaben or flutemetamol PET radioligands and tau burden as measured by [^{18}F] GTP1 (an investigational radioligand for in vivo imaging of tau protein aggregates) in

participants with early AD. Details of any interim analyses relating to the substudies will *also* be described in the substudy protocols.

The PET data that are collected are expected to help in understanding the effects of gantenerumab on amyloid and tau pathology over time as well as the relationship between change in florbetaben/flutemetamol/[^{18}F] GTP1-PET and changes in other endpoints in the study WN39658.

Data Monitoring Committee

The iDMC will evaluate participant safety and efficacy on a regular basis. In addition to the data defined in the iDMC Charter (e.g., the incidence and nature of adverse events, serious adverse events, adverse events of special interest, ARIA-E, ARIA-H, and ISRs), the iDMC will review all necessary cumulative data at regular intervals during the study, including efficacy when needed. It is anticipated that these assessments will occur approximately every 3 months. At the time of each review, the iDMC will make appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, the treatment regimen should be modified, the protocol should be amended, enrollment should be held pending further safety evaluations). The iDMC will also evaluate planned or unplanned interim analyses for efficacy or futility.

Decisions will be made in consideration of the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details such as the committee's composition, frequency, and timing of meetings, and members' roles and responsibilities are detailed in the iDMC Charter.

Final decisions will rest with the Sponsor.

Number of Patients

The planned enrollment specifies approximately 1016 participants.

Target Population

This study will enroll approximately 1016 participants with increased brain amyloid burden (defined according to CSF or PET criteria), objective memory impairment indicated by cognitive assessment, and a diagnosis of probable AD or prodromal AD based on relevant NIA/AA criteria during the global enrollment phase.

An increase in sample size may be considered in the event of changes to the sample size assumptions on the basis of blinded data review or factors external to the study.

If at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA during the global enrollment phase, additional participants may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. All participants enrolled at NMPA-recognized sites in the global enrollment phase will be included in the primary analysis. All participants enrolled at NMPA-recognized sites in the global enrollment phase and the China extension phases will be included in a China-specific analysis. Details will be provided in the SAP.

Inclusion Criteria

Participants must meet the following criteria for study entry:

- Ability to provide written consent signed by the participant (co-signed by the participant's legally authorized representative, if required by the local regulations, guidelines, and independent Ethics Committee or Institutional Review Board)
- Age 50–90 years old at screening, inclusive
- Availability of a person (referred to as the "study partner" throughout this protocol) who:
  - Agrees to participate throughout the duration of study
  - In the investigator's judgment, has frequent and sufficient contact (e.g., 5 times per week or approximately 10 hours per week) with the participant
  - In the investigator's judgment, is able to provide accurate information regarding the participant's cognitive and functional abilities, including knowledge about domestic activities, hobbies, routines, social skills, and basic activities of daily life; work and educational history; cognitive performance including memory abilities, language abilities,

temporal and spatial orientation, judgment and problem solving; emotional and psychological state; and can report any changes in the general health status

- Agrees to provide information and to complete all aspects of the study at clinic visits (which require partner input for scale completion)
- Signs the necessary Informed Consent Form(s), and has sufficient cognitive capacity to accurately report on the participant's behavior as well as cognitive and functional abilities
- Is fluent in the language used at the site and has sufficiently good general health to have a high likelihood of maintaining the same level of interaction with the patient and participation in study procedures throughout the duration of the study

Every effort should be made to have same study partner participate throughout the duration of the study.

- Fluency in the language of the tests used at the study site
- Willingness and ability to complete all aspects of the study (including MRI, lumbar puncture [if applicable], clinical genotyping, and PET imaging [if applicable])

  The participant should be capable of completing assessments either alone or with the help of the study partner.
- Adequate visual and auditory acuity, in the investigator's judgment, sufficient to perform the neuropsychological testing (eye glasses and hearing aids are permitted)
- Evidence of AD pathological process, as confirmed by CSF tau/$A\beta_{42}$ or on amyloid PET scan by qualitative read by the core/central PET laboratory
- Demonstrated abnormal memory function at screening (FCSRT cueing index ≤ 0.67 and free recall ≤ 27)
- Screening MMSE score ≥ 22 and CDR-GS of 0.5 or 1.0
- Probable AD dementia (consistent with NIA/AA core clinical criteria for probable AD dementia) or prodromal AD (consistent with the NIA/AA diagnostic criteria and guidelines for mild cognitive decline due to AD)
- If the participant is receiving symptomatic AD medications, a stable dosing regimen for at least 3 months prior to screening and until randomization
  - Participants receiving GV-971 or who are planning to take GV-971 during the study are not eligible
- Agreement not to donate blood or blood products for transfusion for the duration of the study and for 1 year after final dose of study drug
- Agreement not to participate in other research studies for the duration of this trial and its associated substudies
- For enrollment in the China extension, participants must have residence in mainland China, Hong Kong, or Taiwan and be of Chinese ancestry
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 16 weeks after the last dose of study drug

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

Exclusions Related to Central Nervous System Disorders

Participants who meet any of the following criteria related to CNS disorders will be excluded from study entry:

- Any evidence of a condition other than AD that may affect cognition, including, but not limited to, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, Parkinson disease, corticobasal syndrome, Creutzfeldt-Jakob disease, progressive supranuclear palsy, frontotemporal lobar degeneration, Huntington disease, normal pressure hydrocephalus, seizure disorder, delirium or hypoxia
- History or presence of clinically evident systemic vascular disease (e.g., clinically significant carotid/vertebral artery stenosis or plaque, aortic aneurysm), that in the opinion of the investigator has the potential to affect cognitive function
- History or presence of clinically evident cerebrovascular disease (e.g., intracranial or cerebral vascular malformations, aneurysm, intracranial macrohemorrhage)

  Participants with asymptomatic developmental venous anomalies may be eligible after discussion with and approval by the Medical Monitor.
- History or presence of posterior reversible encephalopathy syndrome
- History or presence of any stroke with clinical symptoms within the past 12 months, or documented history within the last 6 months of an acute event that is consistent, in the opinion of the investigator, with a transient ischemic attack
- History of severe, clinically significant (persistent neurologic deficit or structural brain damage) CNS trauma (e.g., cerebral contusion)
- History or presence of intracranial mass (e.g., glioma, meningioma) that could potentially impair cognition
- Presence of infections that affect brain function or history of infections that resulted in neurologic sequelae (e.g., HIV, syphilis, neuroborreliosis, and viral or bacterial meningitis and encephalitis)
- History or presence of systemic autoimmune disorders that potentially cause progressive neurologic disease with associated cognitive deficits (e.g., multiple sclerosis, lupus erythematosus, anti–phospholipid antibody syndrome, and Behçet disease)
- History of schizophrenia, schizoaffective disorder, major depression, or bipolar disorder

  History of major depression is acceptable if participant has had no episode within the past year or is considered in remission or depression is controlled by treatment.
- At risk for suicide in the opinion of the investigator
- Alcohol and/or substance abuse or dependence (according to the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, Version 5) within the past 2 years

  Nicotine use is allowed.

  Marijuana use is not allowed and must be discontinued at least 3 months before screening.

Imaging-Related Criteria

Participants who meet any of the following imaging criteria will be excluded from study entry:

- According to the MRI central reader, MRI evidence of any of the following:
  - $>$ 2 lacunar infarcts
  - Any territorial infarct $>$ 1 cm^3
  - Any white matter lesion that corresponds to an overall Fazekas score of 3 that requires at least one confluent hyperintense lesion on the fluid-attenuated inversion recovery (FLAIR) sequence, which is $\geq$ 20 mm in any dimension

- Combined number of microbleeds and areas of leptomeningeal hemosiderosis (i.e., cumulative ARIA-H) on MRI more than five (and should not include any disseminated leptomeningeal hemosiderosis) based on the review performed by the central reader prior to randomization
- Presence of any other significant cerebral abnormalities, including ARIA-E, as assessed on MRI
- Inability to tolerate MRI procedures or contraindication to MRI, including, but not limited to, presence of pacemakers not compatible with MRI, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan, or any other clinical history or examination finding that, in the judgment of the investigator, would pose a potential hazard in combination with MRI

Cardiovascular Disorders

Participants who meet any of the following criteria related to cardiovascular disorders will be excluded from study entry:

- History or presence of clinically symptomatic atrial fibrillation requiring maintenance therapy

  Participants who experienced non-valvular atrial fibrillation that resolved more than 1 year ago and was not associated with prior stroke are eligible.
- Within the last year, unstable or clinically significant cardiovascular disease (e.g., myocardial infarction)

  Heart failure classified as New York Heart Association Class I or II cardiac disease is allowed if not associated with hospitalization within the previous 12 months.
- Uncontrolled hypertension (e.g., blood pressure generally >160 mmHg systolic or >95 mmHg diastolic)

Hepatic and Renal Disorders

Participants who meet any of the following criteria related to hepatic and renal disorders will be excluded from study entry:

- Chronic kidney disease, indicated by creatinine clearance <30 mL/min to be calculated by the central laboratory using the Cockcroft-Gault formula at screening, which remains <30 mL/min if retested
- Confirmed and unexplained impaired hepatic function as indicated by screening AST or ALT $\geq 3\times$ the upper limit of normal (ULN) or total bilirubin $\geq 2\times$ ULN

Infections and Immune Disorders

Participants who meet any of the following criteria related to infections and immune disorders will be excluded from study entry:

- History of, or known to currently have HIV infection, or hepatitis B or hepatitis C infection that has not been adequately treated in the opinion of the investigator, or history of spirochete infection of the CNS (e.g., syphilis, Lyme disease, or borreliosis)
- Systemically, clinically significantly immunocompromised participants, owing to continuing effects of immune-suppressing medication

Metabolic and Endocrine Disorders

Participants who meet any of the following criteria related to metabolic and endocrine disorders will be excluded from study entry:

- Abnormal thyroid function as indicated by abnormal screening tests that are judged to be clinically significant by the investigator, or abnormal thyroid function that requires a new treatment or an adjustment of current treatment

  A participant may be rescreened if there is no improvement in cognition in the investigator's judgment after 3 months of adequate treatment for thyroid function.

- Participants with evidence of folic acid deficiency (as indicated by folic acid level below the lower limit of normal) or vitamin B-12 deficiency (as indicated by vitamin B-12 level below the lower limit of normal and/or methylmalonic acid levels above ULN)

  A participant may be rescreened if there is no improvement in cognition after 3 months of adequate treatment for folic acid or vitamin B-12 deficiency.
- Screening hemoglobin A_{1c} (HbA_{1C}) $>$ 8% (retesting is permitted if slightly elevated) or poorly controlled insulin-dependent diabetes (including hypoglycemic episodes)

  A participant may be rescreened after 3 months to allow optimization of diabetic control.

Exclusions Related to Medications

The following medications are prohibited for a pre-specified duration prior to study start, as indicated, and during the entire period of study participation (participants who start these medications during the study may be withdrawn from study treatment):

- Any previous administration of gantenerumab or active immunotherapy (vaccine) that is being evaluated to prevent or postpone cognitive decline
- Any passive immunotherapy (immunoglobulin) or other long–acting biologic agent that is under evaluation to prevent or postpone cognitive decline within 1 year of screening
- Any other investigational treatment or any other treatment with a monoclonal antibody within 5 half-lives or 4 months prior to screening, whichever is longer
- Any previous administration of GV-971
- Any previous treatment with medications specifically intended to treat Parkinson symptoms or any other neurodegenerative disorder within 1 year of screening and with no plans to initiate such medications prior to randomization

  Certain medications are acceptable if the participant is taking the medicine for a non-neurodegenerative disorder, such as restless leg disorder (e.g., pramipexole).
- Typical antipsychotic or neuroleptic medication within 6 months of screening and with no planned changes prior to randomization except as brief treatment for a non-psychiatric indication (e.g., emesis)

  Atypical antipsychotic medications are not allowed except for intermittent short-term use and will need to be discontinued 2 days or at least 5 half-lives (whichever is longer) prior to any neurocognitive assessment.
- Anticoagulation medications within 3 months of screening with no plans to initiate any prior to randomization

  Anti-platelet treatments (e.g., aspirin, clopidogrel, and dipyridamol) are permitted.

  Short-term, perioperative use of anticoagulant medications will not result in permanent discontinuation from the study; however, *for* any such use *it is recommended to* prospectively *seek advice from* the Medical Monitor and temporary study drug interruption *may be required*.
- Chronic use of opiates or opioids (including long-acting opioid medication) within 3 months of screening with no plans to initiate any prior to randomization

  Intermittent short-term use of short–acting opioid medications for pain is permitted except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.
- Stimulant medications (amphetamine, methylphenidate preparations, or modafinil) within 1 month of screening and throughout the study
- Chronic use of benzodiazepines, barbiturates, or hypnotics from 3 months before screening and with no plans to initiate any prior to randomization

  Intermittent short-term use of benzodiazepines, buspirone, or short-acting hypnotic medication for sleep or anxiety is allowed except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

Other Exclusions

Participants who meet any of the following criteria will be excluded from study entry:

- Other causes of intellectual disability that may account for cognitive deficits observed at screening (e.g., static encephalopathy, closed brain injury, mental retardation)

  This may be based on, for example, the participant's sufficient education or work experience.
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study
- Deformity of the lumbosacral region of the spine that in the opinion of the investigator would contraindicate lumbar puncture in participants who will have lumbar puncture
- Clinically significant abnormal screening blood, CSF (if applicable), or urine results that remain abnormal at retest
- Impaired coagulation (screening prothrombin time [PT] $> 1.2 \times$ the ULN that remains abnormal on retest)
- History of cancer, with the following exceptions:
  - If considered to be cured
  - If not being actively treated with anti-cancer therapy or radiotherapy and, in the opinion of the investigator, is not likely to require treatment in the ensuing 5 years
  - For prostate cancer or basal cell carcinoma, no significant progression over the previous 2 years
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins, including gantenerumab
- Hypersensitivity to any of gantenerumab excipients
- Any other severe or unstable medical condition that, in the opinion of the investigator or Sponsor, could be expected to progress, recur, or change to such an extent that it could put the participant at special risk, bias the assessment of the clinical or mental status of the participant to a significant degree, interfere with the participant's ability to complete the study assessments, or would require the equivalent of institutional or hospital care
- Residence in a skilled nursing facility such as a convalescent home or long-term care facility: Participants who subsequently require residence in such facilities during the study may continue in the study and be followed for efficacy and safety, provided that they have a study partner who meets the minimum requirement

Eligibility for the Open-Label Extension

Participants who have been randomized and who have completed the double-blind treatment period will be eligible to participate in the OLE, provided they do not meet any of the following criteria:

- Discontinued from study treatment during the double-blind treatment period
- Received any other investigational medication during the double-blind treatment period or after the end of double-blind treatment
- Participation in the OLE deemed inappropriate by the investigator (e.g., any serious medical condition or other concerns that preclude the participant's safe participation in the OLE or ability to comply with the required procedures)
- Presence of ARIA-E findings at the Week *116 (or Week 128, if applicable)* MRI scan (participants who have ongoing ARIA-E findings at the Week *116 [or Week 128, if applicable])* MRI scan will stay in the double-blind treatment period until the finding is deemed resolved). *For those participants who enroll into the GRADUATE OLE from Week 104, before the double-blind extension took place, eligibility for the OLE would be based on the Week 104 scan.*

End of Study

The end of the study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for safety analyses or safety follow-up is received for the last participant, whichever occurs later.

Length of Study

The study will consist of a screening period of up to 12 weeks (including the optional prescreening period) for each eligible participant who signs the Informed Consent Form and agrees to participate, followed by a double-blind treatment period of study drug treatment plus a visit 2 weeks after the last dose. The duration of the double-blind treatment period is extended by 12 weeks (116 weeks in total in scenario 1). In case scenario 2 is implemented, the double-blind treatment period will be extended by 24 weeks (128 weeks in total in scenario 2, if applicable). For participants not entering the OLE period, this will be followed by the post–double-blind treatment period of two follow-up visits at 14 and 50 weeks after the last dose. Thus, for a participant not entering the OLE period, the maximum length of study is approximately 176 weeks in scenario 1 or 188 weeks in scenario 2 (if applicable).

For participants entering the OLE period, the extension will consist of an open-label period of at least 35 weeks. If a participant is ready to be uptitrated to the target dose and if the safety MRI allows, the participant will then be transitioned to the WN42171 open-label study. If there is an ongoing ARIA-E, the participant will remain in Study WN39658 until the ARIA-E resolves and the participant is ready to be uptitrated to the target dose. In case the dosing is temporarily interrupted for any other reason, the participant will be kept in the WN39658 study until they are ready to be uptitrated to the target dose. Participants who are not willing to transition to the WN42171 open-label study after OLE Week 35 will be asked to come back for two follow-up visits at 14 and 50 weeks after the last dose (OLE Follow Up 1 and Follow Up 2, respectively).

Investigational Medicinal Products

The investigational medicinal product (IMP) for this study is gantenerumab.

Test Product (Investigational Drug)

Gantenerumab or placebo will be administered by SC injection to all participants.

Double-Blind Treatment Period

Gantenerumab will be administered by SC injection to all patients randomized to the active treatment arm, regardless of *APOE* ε4 status, at a dose of 120 mg SC Q4W for 3 months, 255 mg SC Q4W for 3 months, and 510 mg SC Q4W for 3 months, prior to reaching the target dose. Once the target dose is reached, study drug will be administered every 2 weeks (Q2W administration of 510 mg SC gantenerumab). The switch to a Q2W administration schedule allows decreasing the number of SC administrations in the abdomen per visit.

Note: A minimum of 3 doses during each dosing step must be administered prior to uptitration.

For Q4W injections, a time window of ±7 days is allowed for dosing visits. For Q4W injections, the recommended minimum time between doses is 3 weeks. The maximum recommended time between doses should not exceed 6 weeks. Once study drug is administered Q2W, the time window for dosing visits is ±3 days. For Q2W injections, the recommendation is not to administer more than 1020 mg (i.e., 2 times 510 mg Q2W) within 28 days. Always return to the initial planned schedule per randomization for subsequent visits.

Regardless of dose, each participant will undergo up to a total of 49 dosing visits in scenario 1 or 55 dosing visits in scenario 2 (if applicable) in the double-blind treatment period of the study. Participants who have completed the double-blind treatment period at the time of the implementation of *the 12 week study extension*, will have undergone up to 43 dosing visits. Injections will be administered as one 0.8-mL (120-mg dose), one 1.7-mL (255-mg dose), or two 1.7-mL injections (510-mg dose) subcutaneously to the abdomen, respectively.

Placebo of identical composition (except protein) and identical volume to gantenerumab will be administered by SC injection to all participants randomized to placebo at the same frequency and using the same route of administration.

On study drug administration days that include efficacy assessments, study drug must be administered at the clinical site. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

At applicable sites, study drug may be administered by a trained nursing professional at the participant's home or another suitable location, if the participant has given written informed consent to participate in home nursing visits.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Open Label Extension Period

During the OLE, participants previously randomized to the active treatment arm will continue to be administered the study drug every two weeks (Q2W administration of 510 mg SC gantenerumab). Participants previously randomized to the placebo arm will be required to undergo 9 months of uptitration.

In order to maintain the previous study treatment blinding (Sponsor, site, and participant), all participants will be dosed every two weeks in the OLE. As in the double-blind treatment period, a safety MRI has to be performed before each uptitration to ensure that the participant can be uptitrated safely to the next dose.

To ensure blinding to previous treatment, administration will consist of one 0.8-mL and two 1.7-mL injections for the 120-mg dose or will consist of two 1.7-mL injections for the 255 mg dose and 510-mg dose. Injections will be administered subcutaneously to the abdomen.

Note: As in the double-blind part, a minimum of 3 doses during each dosing step must be administered prior to uptitration. During uptitration in the OLE, a minimum of 3 doses of each dosing step also have to be administered prior to be eligible for uptitration. In the OLE, a dose is defined as two consecutive dosing visits (one with an even dose number and one with an odd dose number).

For the OLE, the time window for dosing visits is $\pm$ 3 days. Always return to the initial planned schedule per randomization for subsequent visits.

Participants enrolled in the WN39658 OLE study will have to complete the full titration scheme (i.e., at least 12 weeks on each dosing step) prior to being able to enroll in the WN42171 open-label study where they will receive 510 mg SC Q2W.

On study drug administration days that include efficacy assessments (see the schedule of activities in Appendix 1), study drug must be administered at the clinical site. Study personnel who prepare and administer the study drug must not be involved with any efficacy assessments or safety evaluations.

At applicable sites, study drug may be administered by a trained nursing professional at the participant's home or another suitable location if the participant has given written informed consent to participate in home nursing visits.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

PET Tracers

All participants who are enrolled in PET substudies will be assessed by PET imaging using an appropriate PET ligand. For screening, the possible amyloid PET ligands will be florbetapir, florbetaben, and flutemetamol. According to E.U. guidance, the PET tracers as used in the context of this study, are designated as non-IMP. In some regions, according to local regulations, these PET tracers may be considered to be IMP.

In countries where the PET radioligands are approved for marketing, the approved local product information will be provided, and in countries where they are not approved for marketing, the Investigator's Brochures will be provided.

Details about the PET substudies are described in separate protocols.

Statistical Methods

Primary Analysis

The primary efficacy outcome measure is the change in CDR-SOB from baseline (Day 1) to Week 116. In the case where the double-blind treatment period is extended for an additional 12

weeks, the primary efficacy outcome measure will be the change in CDR-SOB from baseline (Day 1) to Week 128.

The clinical question of interest is to assess the study treatment effect on disease progression up to Week 116 (or Week 128, if applicable), irrespective of use or initiation of symptomatic treatments for AD, in the absence of the COVID-19 pandemic.

In accordance with the estimand framework outlined in the ICH-E9 addendum (EMA 2018), the attributes of the estimand for the primary endpoint are defined as follows:

- *Population: early (prodromal to mild) AD population including all randomized participants.*
- *Variable: change from baseline at Week 116 (or Week 128) in the CDR-SOB.*

  Treatment: prescribed study drug including uptitration to the target dose, irrespective of use or initiation of symptomatic treatment for AD.
- *Intercurrent events (ICE): the list of ICE will be defined in the SAP, this includes:*

  Treatment discontinued for study drug or condition–related (SDCR) reasons (e.g., treatment-related adverse event or lack of efficacy):

  Treatment discontinued for non-study drug or condition–related reasons (NSDCR) reasons (e.g. purely administrative reason).
- *Population level summary: mean change from baseline to Week 116 (or Week 128, as appropriate) between gantenerumab-treated participants and placebo-treated participants.*

The primary estimand is a combination of a treatment-policy strategy and a hypothetical strategy (FDA 2017) to account for the different assumptions for each type of ICE. Full details of the primary estimand, and of the corresponding estimator and estimation methods (e.g. statistical model, multiple imputation for missing or excluded data points) will be provided in the SAP. Supplementary estimands may also be considered and will be defined in the SAP.

Every effort will be made to minimize missing data. Furthermore, the Sponsor *has made* every effort to expedite the implementation *of the 12 week extension* to the double-blind treatment period. If the study is extended by an additional 12 weeks (for a total extension of 24 weeks), the number of patients in scenario 1 (who will have missing Week 128 efficacy data) will be minimized.

Participants who discontinue early from study treatment will be asked to return for collection of safety and limited efficacy data (i.e., the primary and secondary efficacy endpoints) until the end of the double-blind treatment period and follow-up visits. To explore the robustness of MMRM results for the primary efficacy conclusions sensitivity analyses (e.g., using multiple imputation and pattern mixture models) will be performed. Descriptive summaries of the number of participants with missing data, the number of participants in each scenario, the timing, and reasons for discontinuation from the study will also be provided by treatment group.

Determination of Sample Size

Determination of sample size is based on participants enrolled in the global enrollment phase. In this study, approximately 1016 participants will be enrolled and randomized in 1:1 ratio to each treatment arm (gantenerumab or placebo) during the global enrollment phase. A sample size increase may be considered if factors external to the study or blinded study data review would warrant a change to the sample size assumptions.

Additional participants may be randomized during the China extension if at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA during the global enrollment phase.

The estimated sample size required to demonstrate efficacy with regard to CDR-SOB is based on the following assumptions:

- The mean change in the CDR-SOB from baseline to Week 104 is 2.5 points in the placebo arm
- A common standard deviation across treatment arms for change of approximately 2.97 from baseline to Week 104 in the CDR-SOB
- Gantenerumab has a true effect of a 30% relative reduction in deterioration of CDR-SOB

Based on these assumptions, and using a student's T-test with equal variance, a sample size was calculated for 90% power to detect a true treatment effect of 30% relative reduction in deterioration of CDR-SOB at a two-sided α of 0.05.

Uncertainties on parameters affecting the power (e.g., dropout rate, study drug discontinuation rate, standard deviation, and placebo decline) were assumed to be equivalent to a drop-in sample size of up to around 35% and were corrected for accordingly. This calculation leads to a total of 1016 participants in the study.

At the date of writing Protocol Version 4, it is expected that participants *would have missed* an average of 8 weeks of study drug administration over the course of the original 2-year study due to the COVID-19 pandemic. This has the potential to decrease the power of the study from ~90% to ~80%. To mitigate the impact of missed administrations, the double-blind treatment period *was* extended by 12 weeks. Under current assumptions, this brings the study power back to the originally planned ~90%.

The sample size may be increased from 1016 up to 1322 participants (661 participants per arm). The decision whether to increase sample size will be based on blinded study data review, e.g., by a review of the frequency of missed study drug administrations due to the COVID-19 pandemic. Further details will be described in the SAP. The assessment will be performed by the Sponsor at a specified timepoint. The sponsor will remain blinded. The sample size will not be reduced on the basis of this assessment. Other factors external to the study may also trigger a decision to increase sample size.

Interim Analyses

Optional Futility Analysis

The Sponsor may perform an interim analysis for futility approximately 116 weeks after 50% of the targeted study enrollment has been reached. If the study is extended by an additional 12 weeks, the interim analysis will be performed approximately 128 weeks after 50% of the targeted study enrollment has been reached. The exact timing of an interim analysis may be synchronized with study WN29922.

An independent data coordinating center will be responsible for the interim analyses. The study results will only be reviewed by the iDMC and the Sponsor will remain blinded. *Other third party vendors may be involved in the data preparation and analyses, as appropriate.*

The iDMC may recommend *to* stop for futility if the failure criterion is met. The failure criterion will represent a low probability of a positive study outcome given the data observed at the time of interim analysis. *If the futility criteria are not met, the study continues beyond the interim analysis.* The failure criterion will be prespecified in the iSAP.

Details of the futility analysis, including the final decision to conduct it, the rationale, timing, and statistical details for the analyses (such as the data that would be reviewed by the iDMC and futility thresholds) will be documented in the iSAP. This will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.

Optional Interim Analyses

Based on availability of information pertaining to gantenerumab or other compounds with similar mode of action that may emerge during the course of this study, the Sponsor may choose to conduct an additional interim analysis*, which may include efficacy, safety and biomarker outcomes including amyloid PET SUVr and/or other biomarkers to confirm PD effect. This analysis may be done on a whole study population or in a well predefined subgroup when approximately 50% of the overall population has reached Week 116. If the study is extended by an additional 12 weeks, the interim analysis will be performed once approximately 50% of the overall population has reached Week 128.*

An independent data coordinating center will be responsible for the interim analyses. The study results will only be reviewed by the iDMC and the Sponsor will remain blinded. *Other third party vendors may be involved in data preparation and analyses, as appropriate.*

The iDMC may indicate that a pre-specified success criterion has been met. If so, the Sponsor may decide to present the data to a health authority. Any interim, unblinded data will be strictly firewalled to ensure those involved in the conduct of the ongoing trial and the WN42171 OLE trial remain fully blinded. If needed, appropriate measures will be taken to control the overall Type I error rate and described in the SAP.

Details of the interim analyses, including the decision to conduct the optional interim analysis, the rationale, timing, and statistical details for the analyses (such as the data that would be reviewed by the iDMC and futility or efficacy thresholds) will be documented in the SAP, and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Aβ	amyloid-beta
AD	Alzheimer's disease
ADA	anti-drug antibody
ADAS-Cog11	Alzheimer's Disease Assessment Scale–Cognition, Subscale 11
ADAS-Cog13	Alzheimer's Disease Assessment Scale–Cognition, Subscale 13
ADCS-ADL	Alzheimer's Disease Cooperative Study Group–Activities of Daily Living
ADL	activities of daily living
APOE ε4	apolipoprotein E, allele ε4
ARIA	amyloid-related imaging abnormality
ARIA-E	amyloid-related imaging abnormality–edema/effusion
ARIA-H	amyloid-related imaging abnormality–hemosiderin deposition
AUC	area under the concentration–time curve
AUC_{inf}	area under the concentration–time curve from Time 0 to infinity
BOLD	blood oxygenation level-dependent
BGTS	Barkhof grand total score
CDR	Clinical Dementia Rating
CDR-GS	CDR global score
CDR-SOB	Clinical Dementia Rating–Sum of Boxes
C_{max}	maximum concentration
CNS	central nervous system
COA	clinical outcome assessment
CRO	contract research organization
CSF	cerebral spinal fluid
C-SSRS	Columbia–Suicide Severity Rating Scale
CT	computed tomography
CTAD	Clinical Trials in Alzheimer's Disease
DTI	diffusion tensor imaging
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
EQ-5D	EuroQol-Five Dimensions questionnaire

Abbreviation	Definition
FA	fractional anisotropy
FA	fractional anisotropy
FAQ	Functional Activities Questionnaire
FCSRT	Free and Cued Selective Reminding Test
FCSRT-IR	Free and Cued Selective Reminding Test–Immediate Recall
FDA	(U.S.) Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
GRE	gradient recalled echo
HbA_{1C}	hemoglobin A_{1c}
HIPAA	Health Insurance Portability and Accountability Act
HN	home nursing
ICH	International Council on Harmonisation
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ISR	injection-site reaction
ITT	intent to treat
IWG	International Working Group
IV	intravenous
IxRS	interactive voice or Web-based response system
LPLV	last patient, last visit
MAD	multiple-ascending dose
MCI	mild cognitive impairment
MMRM	mixed model repeated measure
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NIA/AA	National Institute on Aging/Alzheimer's Association
NMPA	National Medical Products Administration
NPI-Q	Neuropsychiatric Inventory–Questionnaire
NSDCR	*non-study drug or condition-related*
OLE	open-label extension
PD	pharmacodynamic
PET	positron emission tomography
PK	pharmacokinetic
PT	prothrombin time

Abbreviation	Definition
p-tau	phosphorylated tau
QoL	quality of life
QoL-AD	Quality of Life–Alzheimer's Disease
Q2W	every 2 weeks
Q4W	every 4 weeks
RBR	Research Biosample Repository
rs-fMRI	resting-state functional magnetic resonance imaging
RUD-Lite	Resource Utilization in Dementia–Lite
SAD	single-ascending dose
SAP	Statistical Analysis Plan
SC	subcutaneous
SDCR	*study drug or condition-related*
SOB	Sum of Boxes
SUVr	standardized uptake value ratio
t-tau	total tau
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing
ZCI-AD	Zarit Caregiver Interview–Alzheimer's Disease

1. BACKGROUND

1.1 BACKGROUND ON ALZHEIMER'S DISEASE

The World Health Organization estimates that around 50 million people worldwide are diagnosed with dementia and that there are 10 million new cases every year. The total number of people with dementia is estimated to reach 82 million in 2030 and will more than triple by 2050 to 152 million. Alzheimer's disease (AD) is the most common form of dementia, accounting for 60%–70% of cases (World Health Organization 2017). The prevalence of AD increases with age, with a global prevalence of 5%–8% in people 60 years and older. Because of its increasing prevalence, long duration, and high cost of care, AD is expected to continue to represent a major public health problem for decades to come.

There is great inter-individual variability in AD progression with survival dependent on many factors, including age at onset. In general, the clinical picture evolves from "predementia" or "prodromal AD" to mild, moderate, and then severe AD. At the early stage of AD, a slight impairment of memory, language, and visuospatial function can be observed. As AD advances, patients become progressively impaired and the burden on caregivers significantly increases. The median survival time following a diagnosis of AD strongly depends on the patient's age at diagnosis and ranges from 8.3 years for persons diagnosed with AD at 65 years old to 3.4 years for those 90 years old (Brookmeyer et al. 2002). On average, individuals live 3–9 years after diagnosis (Helzner et al. 2008) and some survive as long as 20 years.

It is well recognized that in comparison to other therapeutic domains, there is a real unmet medical need in AD therapy (Gauthier et al. 2016). To date, only five medications have received marketing approval to treat the symptoms of AD, including acetylcholinesterase inhibitors (AChEi) and N-methyl-d-aspartate receptor antagonists. These approved drugs are recognized to temporarily improve some clinical symptoms of AD in some patients but do not modify progression of the disease (Cummings et al. 2016). Recent efforts have mostly focused on therapies targeting amyloid (Bachurin et al. 2017) as these offer the most compelling therapeutic targets (Graham et al., 2017). These therapies are based on the amyloid hypothesis that posits amyloid-β (Aβ) accumulation as the primary factor driving Aβ pathogenesis (Selkoe 1991; Hardy and Selkoe 2002; Selkoe and Hardy 2016). This Aβ accumulation in the brain begins well before the development of clinical dementia in AD and causes a series of downstream events leading to synaptic dysfunction, inflammation, neurodegeneration, and clinical symptoms. For these reasons, treatments that prevent, slow, or decrease the accumulation of brain Aβ are being tested as therapeutic agents in AD.

Preclinical evidence has suggested that monoclonal Aβ antibodies may be able to remove and reduce deposition of Aβ aggregates from the brain. In transgenic animal models of AD, vaccination with Aβ or passive immunization with anti–Aβ antibodies resulted in decreased amyloidosis and in improvement of memory function in some

transgenic models cognitive function (Janus et al. 2000). Accumulating clinical evidence also supports that monoclonal Aβ antibodies can bind Aβ and promote its clearance (Salloway et al. 2009; Ostrowitzki et al. 2012), reduce deposition of Aβ aggregates, and reduce markers of neurodegeneration in the cerebral spinal fluid (CSF) (Roche Research Report No. 1066251). In a Phase I study, reduction of deposited amyloid as shown on brain amyloid positron emission tomography (PET) imaging was associated with a time and dose-related slowing of cognitive decline (Sevigny et al. 2016). Because the neurological changes associated with AD develop decades before clinical symptoms emerge, it is thought that earlier intervention may be more effective in arresting or delaying disease progression (Sevigny et al. 2016). Consequently, therapies targeting this process have the potential to significantly alter the progression of the disease. Gantenerumab, a fully human monoclonal antibody targeting aggregated forms of Aβ-like Aβ oligomers, fibrils, and plaques, is expected to address this need (Bohrmann et al. 2012).

1.2 BACKGROUND ON GANTENERUMAB

Gantenerumab (or RO4909832) is a fully human anti−Aβ peptide antibody developed by in vitro selection utilizing aggregated Aβ and in vitro maturation within a complete human Igγ, subclass-1 framework (IgG1). Gantenerumab recognizes a conformational epitope of Aβ present in aggregated Aβ and that is demonstrated for both major species of Aβ that is, $Aβ_{1-40}$ and $Aβ_{1-42}$. Gantenerumab has a molecular mass of 146.3 kDa. In vitro, gantenerumab recognizes synthetic aggregated Aβ fibrils and Aβ oligomers with high nanomolar affinity (K_D, ~0.6−1.2 nM). Based on additional in vitro studies and studies in animal models, the pharmacologic profile suggests that in humans, gantenerumab may prevent, inhibit, and reduce accumulation of Aβ, which is believed to play an important role in the pathogenesis of AD.

Gantenerumab is manufactured by cell culture of a recombinant Chinese hamster ovary−K1 mammalian cell line and subsequent purification of the antibody. The gantenerumab drug substance manufacturing was optimized during development, leading to several manufacturing processes (G1, G2, and G3). Recently, the gantenerumab manufacturing process was further optimized from G3 to G4 to improve process robustness and increase overall process yield. Drug material manufactured by G4 process is used in Phase III clinical trials (e.g., Study WN39658). Gantenerumab is in clinical development for patients with early (prodromal to mild) AD and is also being investigated in carriers of familial AD mutations (DIAN-TU) (Bateman et al. 2017).

Refer to the gantenerumab Investigator's Brochure for details on nonclinical and clinical studies.

1.2.1 Nonclinical Studies

1.2.1.1 Nonclinical Pharmacology

The binding characteristics of gantenerumab were engineered to achieve specific and highly sensitive recognition of the assembly structure of aggregated human $A\beta_{1-42}$ and $A\beta_{1-40}$ peptides, which are major components in Aβ plaques. Specificity was demonstrated ex vivo for genuine human Aβ plaques in AD brain slices. The minimum effective concentration for staining of human Aβ plaques is 10 ng/mL (0.07 nM).

Gantenerumab showed a concentration-dependent increase in cellular phagocytosis of human Aβ plaques by human primary cells like microglia and differentiated macrophages in a brain-slice phagocytosis assay. The measured minimal effective concentration of 10 ng/mL (0.07 nM) is consistent with the observed efficacy for human Aβ plaque binding.

In single-dose and multiple-dose studies, effective brain penetration and binding to Aβ plaques in vivo were demonstrated in various models of AD-related amyloidosis, such as the PS2APP transgenic mouse model. Gantenerumab showed significant and accumulative binding to Aβ plaques. The data indicate that there is no requirement for continuous high peripheral levels to achieve a sustained binding of gantenerumab to amyloid plaques.

The plaque binding of gantenerumab from several manufacturing processes has been evaluated. The degree of plaque binding for gantenerumab manufactured by the G1 and G2 processes was investigated by semi-quantitative fluorescence imaging and was comparable in a 2-week IV safety study in PS2APP transgenic mice at doses of 0, 2, 10, and 40 mg/kg every 3 days.

An additional study, which compared the plaque binding of gantenerumab from the G3 and G4 manufacturing processes following single IV administration to PS2APP transgenic mice at a dose level of 40 mg/kg and assessed by semi-quantitative fluorescence imaging after 7 days, indicated slightly increased target engagement of the G4 material consistent with observed differences in exposure (see Section 1.2.1.2).

Chronic treatment with gantenerumab showed significant efficacy by halting progression of amyloidosis in transgenic PS2APP, APP_{London}, and tau PS2APP mouse models of AD. Amyloid reduction was evident by prevention of new plaque formation and removal of preexisting amyloid plaques by engaging microglia cells.

1.2.1.2 Nonclinical Pharmacokinetics and Metabolism

The pharmacokinetics of gantenerumab were studied in mice, rats, and cynomolgus monkeys following IV administration. Gantenerumab pharmacokinetics were characterized by a rapid initial decrease in plasma levels during the first 24 hours, followed by a long half-life, ranging from 4 to 13 days in all species. Overall, the studies demonstrate that gantenerumab has PK properties similar to other IgGs.

The pharmacokinetics of gantenerumab were also studied following SC administration in cynomolgus monkeys and mice. In cynomolgus monkeys, maximum plasma levels were reached after 3 days. The average bioavailability was estimated at 76%.

Gantenerumab was shown to penetrate the brain in both the monkey and mouse. Brain penetration in the monkey was evident from analysis of CSF samples. The CSF to plasma ratios ranged from 0.006% to 0.018%. Penetration and binding to $A\beta_{1-42}$ plaques in the mouse brain were evident from immunostaining for gantenerumab of brain sections obtained from PS2APP mice dosed with gantenerumab.

Rat PK studies have been conducted to compare the pharmacokinetics of gantenerumab derived from different manufacturing processes (G1, G2, G3, and G4).

Following IV administration to rats, the pharmacokinetics of the G1 and G2 materials were similar. The area under the concentration–time curve (AUC) of the G2 material was slightly lower and accounted for about 80% of the of the G1 material. Although standard bioequivalence criteria for AUC were not met, the observed difference in AUC was not considered to have an impact on the use of the G2 material in further clinical development as the difference in AUC is small. The average terminal half-life of both materials was comparable (8.0 and 8.8 days for the G1 and G2 materials, respectively).

A study comparing the pharmacokinetics of gantenerumab derived from the G3 and G4 manufacturing processes showed that the AUC of G3 material (used in the ongoing Phase III OLE studies WN25203 and WN28745) was lower compared with the G4 material that will be used in Study WN39658 (mean±SD: 932±196 and 1270±187 (μg• hr/mL)/(mg/kg), respectively. The average terminal half-life of both materials was similar (11.5 and 12.3 days for G3 and G4 materials, respectively).

1.2.1.3 Toxicology and Safety Pharmacology

Potential adverse effects in relation to the presence and destruction of $A\beta_{1-42}$ plaques were assessed in PS2APP transgenic mice that were treated with up to 375 mg/kg/wk of IV gantenerumab for up to 26 weeks. No evidence of inflammatory reaction in general or other adverse effects were observed in these studies. Decreases in neutrophils and protein (albumin) that were not considered adverse were seen in mice. As a compensatory response, myeloid hyperplasia in the bone marrow was inconsistently detected in some animals. The reason for the low neutrophil counts is unclear but may be a mouse-specific effect of gantenerumab on neutrophils. Indeed, no such finding was

observed in long-term nonclinical (murine and monkey) and clinical studies, and there have been no symptoms indicating immunosuppression in either species.

In cynomolgus monkeys, gantenerumab was well tolerated in repeat-dose IV toxicity studies of 13 and 26 weeks in duration (3, 10, and 20 mg/kg) and in SC toxicity studies of 13 weeks in duration (20 mg/kg) and 39 weeks in duration (up to 375 mg/kg). In the 26-week toxicity study, in which gantenerumab was administered once weekly, one male monkey in Group 2 (3 mg/kg) was found dead 24 hours after receiving the 26th dose (Day 177). The death was not considered to be related to gantenerumab treatment but rather to a bacterial infection detected on histopathology. There was no treatment-related effect on hematologic parameters (i.e., neutrophil counts) in studies in cynomolgus monkeys.

In the absence of any adverse treatment-related effect in the 39-week toxicity study, a no-observed-adverse-effect level of 375 mg/kg/wk was established, which correlated with a mean maximum concentration (C_{max}) of 2535 μg/mL (male and female animals combined) and a mean area under the concentration–time curve from Time 0 to 168 hours ($AUC_{0-168hr}$) of 386,000 μg • hr/mL (male and female animals combined).

Reproductive toxicity studies in transgenic PS2APP mice did not reveal an effect of gantenerumab on fertility, embryo–fetal, or post-natal development.

1.2.2 Clinical Studies

Gantenerumab has been investigated in 10 completed Phase I clinical studies: three single-ascending dose (SAD) studies (BN18726, JP22474, and BP30042) of healthy volunteers and patients with mild to moderate AD, two multiple-ascending dose (MAD) studies (NN19866 and JP22431) of patients with mild to moderate AD, and three bioavailability studies of healthy subjects (one comparing the IV and SC formulations of gantenerumab [Study WP22461], two comparing lyophilized and high-concentration liquid formulations of gantenerumab [Studies WP27951 and BP29113]). In addition, a tolerability study comparing the pain between faster and slower SC administrations of gantenerumab has been completed (Study WP39322).

In order to assess suitability of the G4 material for future Phase III studies, an extended analytical comparability program was conducted followed by the nonclinical studies. Since differences were observed in AUC, a human relative bioavailability study (WP40052) comparing G3 and G4 gantenerumab after SC administration has also been conducted.

A total of 543 subjects have participated in the Phase I studies; of these participants, 406 healthy volunteers and 101 patients with AD have received gantenerumab.
Two Phase III studies designed to examine efficacy and safety of gantenerumab in patients with prodromal AD (Study WN25203) and mild AD (Study WN28745) have been converted to OLE studies. The OLE studies examining the safety and tolerability of

higher doses of gantenerumab in prodromal AD (Study WN25203) and mild AD (Study WN28745) are ongoing.

Results of relevant studies are summarized below. Refer to the Gantenerumab Investigator's Brochure for further information.

In addition, gantenerumab is being investigated in the Dominantly Inherited Alzheimer Network Trial, a Phase II/III study sponsored by the Washington University School of Medicine, examining the safety, tolerability, biomarker status, and efficacy of gantenerumab (as measured by cognition) in patients who are known to have an AD-causing mutation and are therefore at risk for developing AD dementia.

1.2.2.1 Study NN19866

In the MAD study (NN19866), a total of 60 patients (34 males and 26 females) diagnosed with mild to moderate probable AD received multiple IV doses of gantenerumab (doses ranging from 6 mg to 20 mg, 60 mg, and 200 mg) or placebo every 4 weeks (Q4W) for up to 7 months. Owing to amyloid-related imaging abnormalities (ARIAs), or ARIAs of "vasogenic edema" (ARIA-E) and of "hemosiderosis or microbleeds" (ARIA-H), on brain magnetic resonance imaging (MRI) scans that occurred in some patients after two to four doses of 200 mg of gantenerumab in Cohort 4 (200 mg IV Q4W gantenerumab [equivalent to 330 mg SC Q4W] or placebo), it was decided to terminate dosing for all patients on 9 June 2008. The findings resolved spontaneously within 1–4 months after discontinuation of gantenerumab and no patient required treatment.

1.2.2.1.1 Study NN19866: Pharmacodynamic Results in the NN19866-PET Substudy

In a PET substudy of Study NN19866 (NN19866-PET), the effects of gantenerumab on amyloid load in the brain (defined as standardized uptake value ratio [SUVr] of a cortical composite volume of interest over mean cerebellum gray and using ^{11}C-PiB PET) were evaluated in 18 patients (4 in the placebo group, 8 in the 60-mg IV gantenerumab dose group, and 6 in the 200-mg IV gantenerumab dose group) after 6 months. A mean decrease of 14.9% from baseline was observed in the 200-mg gantenerumab dose group, while an increase was seen in the placebo group (mean, 20.9%), with relative stability compared with baseline in the 60-mg group (mean, 5.3%) (Ostrowitzki et al. 2012).

1.2.2.2 Study WN25203

Based on the results from Study NN19866 and from a relative bioavailability study WP27951, the doses of 105 mg SC Q4W (equivalent to 60 mg IV Q4W) and 225 mg SC Q4W (equivalent to 130 mg IV Q4W) were selected for Study WN25203.
Study WN25203 was initially designed as a Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of 105 mg and 225 mg of gantenerumab administered subcutaneously Q4W in

prodromal AD after 2 years of treatment. Randomization was based on apolipoprotein E, allele ε4 (*APOE* ε4) status. Selection of gantenerumab doses was largely driven with the objective of reducing risk of MRI findings (in the context of the clinical understanding of ARIAs at the time of study design) and by pharmacodynamic (PD) results in the MAD study NN19866. Study WN25203 enrolled 799 patients, and 797 patients were treated (the safety-evaluable population). Following a planned interim futility analysis when approximately 50% of patients had completed 2 years of treatment, the study was declared futile and dosing with the originally selected doses (105 mg and 225 mg) was suspended in December 2014. The mean duration of double-blind treatment was 1.73 years.

Safety analyses confirmed ARIAs and injection-site reactions (ISRs) (associated with SC administration) as identified risks of gantenerumab (see Section 1.2.3 for more details). Approximately 90% of patients experienced at least one adverse event, with the incidence comparable between treatment arms. The incidence of serious adverse events was 19.5%, 17.3%, and 16.9% in the placebo, 105-mg gantenerumab, and 225-mg gantenerumab groups, respectively (Ostrowitzki et al. 2017).

Subsequently, the trial has been converted into an OLE study evaluating doses of up to 1200 mg (see Section 1.3.1).

1.2.2.3 Study WN28745

Study WN28745 was initially designed as a Phase III, 2-year, double-blind, placebo-controlled, efficacy, and safety study of gantenerumab in approximately 1000 patients with mild AD. Patients randomized to receive gantenerumab were to follow a slow titration scheme independent of *APOE*-ε4 genotype, starting at 105 mg of SC gantenerumab Q4W for the first 24 weeks, with progression to 225 mg, based on acceptable results of the control MRI scan. Enrollment into the double-blind phase of the study was stopped in November 2015 because of the futility of Study WN25203. When Study WN28745 was stopped, 389 patients had been enrolled and 387 patients had been treated. There were 108 patients who were also enrolled in a PET substudy of brain amyloid imaging (Study WN28745-PET).

In the double-blind phase of Study WN28745, gantenerumab was found to be safe and well tolerated by patients with mild AD. Adverse events were reported for 80.5% of patients in the placebo group and for 82.8% of patients in the gantenerumab groups, respectively. The most commonly reported adverse events across all treatment groups included fall (8.5%), nasopharyngitis (7.5%), headache (7.0%), dizziness (5.7%), ARIA-E (5.4%), and back pain (5.4%). ISRs, ARIA-E, and ARIA-H were reported more commonly in patients in the gantenerumab group than in the placebo group (ISR: 8.3% vs. 1.0%; ARIA-E: 9.4% vs. 1.5%; ARIA-H: 6.3% vs. 4.1%).

Following the WN25203 futility analysis, the study was converted to an OLE study, evaluating the safety and tolerability of gantenerumab at higher doses (up to 1200 mg).

1.2.2.4 OLE Studies WN25203 and WN28745

Additional analyses of Study WN25203 results indicated that higher doses of gantenerumab may achieve clinically relevant effects on cognition and function (see Section 1.3.1). Thus, both Studies WN25203 and WN28745 were converted to OLE studies to provide participants, including those in the placebo group, the opportunity for treatment with higher doses of gantenerumab expected to have a clinically meaningful effect. Doses up to 1200 mg SC Q4W of G3 gantenerumab are being tested, using dosing regimens designed to minimize the risk of ARIAs and taking into account the *APOE* genotype and the previous double-blind treatment and dose.

As of 1 May 2019, 383 patients had been enrolled in the OLE studies WN25203 and WN28745, with 363 patients exposed to G3 gantenerumab doses higher than 225 mg (i.e., more than the highest repeat dose previously tested in AD patients) and 309 patients having reached the OLE target 1200-mg dose. ISRs and ARIAs remain the identified risks for gantenerumab. Continuous monitoring of safety data and MRI findings by the Sponsor has not identified any new safety signal in these ongoing studies. These OLE studies will be ending in 2020, and patients will be provided with an option to enroll in an open-label, rollover study to evaluate the safety and tolerability of long-term administration of gantenerumab (WN41874).

1.2.2.5 Study WP40052

A total of 114 healthy male and female subjects received a single dose of 600 mg of gantenerumab high concentration, liquid formulation (containing gantenerumab manufactured by either G3 or G4 process, N = 57 in each treatment group). The results showed that the plasma exposure in terms of area under the concentration–time curve from Time 0 to infinity (AUC_{inf}) was approximately 1.18 fold higher after SC administration of material manufactured by G4 process compared with material manufactured by G3 process, whereas C_{max} was similar (1.05 fold higher after administration of G4 material). Single-dose SC administration of 600 mg of gantenerumab as G3 or G4 material was safe and well tolerated.

Refer to the Gantenerumab Investigator's Brochure for details on clinical studies.

1.2.3 Safety Overview

Nonclinical characterization of gantenerumab did not show any relevant safety findings. To date, ARIAs and ISRs are the identified risks for gantenerumab. No differences between active and placebo groups have been observed in laboratory parameters, physical and neurological examinations, vital signs, or electrocardiogram (ECG) parameters.

Amyloid-Related Imaging Abnormalities

In the double-blind phase of Study WN25203 (prodromal AD), ARIA events were time, dose, and *APOE* ε4 allele status dependent. The incidence of ARIA-E was 0.8% in the placebo, 6.6% in the 105-mg gantenerumab, and 13.5% in the 225-mg gantenerumab groups. For ARIA-H, the incidence was 13.2% in the placebo, and 22.9% and 16.2% in the 105-mg and 225-mg gantenerumab treatment groups, respectively. The rates of new ARIA-E were highest between 3 and 6 months of treatment (3.8% and 7.5% in the 105-mg and 225-mg gantenerumab groups, respectively) and decreased substantially after the first year of treatment (incidence of up to 2.3% in the 225-mg gantenerumab group in approximately 2 years). The median MRI Barkhof grand total score (BGTS) (Barkhof et al. 2013) of these findings was 3. Most ARIA events were asymptomatic and did not lead to clinically significant consequences. A total of 5 patients (1.8%) from the 105-mg gantenerumab arm and 6 patients (2.3%) from the 225-mg gantenerumab arm experienced symptoms related to ARIA findings; the most commonly reported symptom was headache (5 patients). Other symptoms reported with ARIA-E included visual disturbances (left eye diplopia and upper left quadrantanopia), focal seizure (dysarthria/aphasia that lasted for 10 minutes), anxiety, hyperreflexia, confusional state, disturbance in attention, cognitive disorder, malaise, and dizziness. Symptomatic ARIAs were of mild severity and were non-serious except for one serious adverse event of focal seizure.

Following the futility analysis for Study WN25203, treatment in the double-blind phase was discontinued in July 2017 (median double-blind treatment duration: 68 weeks) and consenting patients transitioned into OLE.

In the double-blind phase of Study WN28745, the frequency of ARIA-E was 1.5% and 11.5% in the placebo and gantenerumab groups, respectively. The frequency of ARIA-H was 11.8% and 15.1% in the placebo and gantenerumab groups, respectively. The median BGTS of ARIA-E was 3. Most ARIAs were asymptomatic and did not lead to clinically significant consequences. Two patients reported CNS adverse events as symptoms of ARIAs: one patient (0.5%) in the placebo group reported irritability that was mild in intensity and non-serious, and one patient (0.5%) in the gantenerumab group reported headache that was moderate in intensity and non-serious.

The WN25203 and WN28745 OLE studies are ongoing and consequently, data are still accruing. As of 1 May 2019, all 154 patients dosed with gantenerumab in the WN25203 OLE study had a post-baseline MRI scan. Of 154 patients, 47 (30.5%) had new ARIA-E (median maximum BGTS of 7.0), and 14 of 154 patients (9.1%) had new ARIA-H without ARIA-E. The majority of ARIA-E findings were asymptomatic, with 11 out of 47 patients with new ARIA-E MRI findings reporting associated CNS adverse events. The CNS adverse events were mostly mild to moderate in intensity, non-serious, and did not require permanent cessation of study treatment. Most symptomatic ARIA-E cases resolved with protocol-defined ARIA management rules. In 3 of the 11 patients with

ARIA-E MRI findings who reported associated CNS adverse events, the events were reported as serious (confusional state, seizure, and epilepsy).

As of 1 May 2019, 219 of 225 patients dosed with gantenerumab in the WN28745 OLE study had a post-baseline MRI scan. Seventy-one of 219 patients (32.4%) had new ARIA-E (median maximum BGTS of 9.0), and 24 of 219 patients (11.0%) had ARIA-H without ARIA-E. The majority of ARIA-E events were asymptomatic, with 18 of 71 patients with ARIA-E MRI findings reporting associated CNS adverse events. The CNS adverse events were mostly mild to moderate in intensity, non-serious, did not require permanent cessation of study treatment, and resolved with protocol-defined ARIA management rules. In 4 of the 18 patients with symptomatic ARIA-E, the events were reported as serious (ischemic stroke, generalized tonic-clonic seizure, epilepsy, and hemiplegia).

Overall, gantenerumab uptitration is associated with a lower rate of ARIA than the predicted rate for fixed dose, and the ARIA-E incidence observed in the OLEs has been in the expected range and in alignment with the ARIA-E PK/PD model. ARIAs are clinically manageable by protocol-defined MRI monitoring and dose intervention algorithms.

Injection-Site Reactions

In the double-blind phase of Study WN25203, the incidence of ISRs was 4.5%, 18.8%, and 23.1% in the placebo, 105-mg gantenerumab, and 225-mg gantenerumab groups, respectively. All ISRs were non-serious, and the majority were mild in intensity and resolved without treatment. The most common signs and symptoms of ISRs included injection-site erythema, pruritus, and rash. Two patients (0.3%) discontinued study treatment due to ISR.

In the double-blind phase of Study WN28745, the incidence of ISRs was 1.0% and 9.4% in the placebo and gantenerumab groups, respectively. All ISRs were non-serious and mild in intensity; the vast majority resolved without treatment. The most common signs and symptoms of ISRs included injection-site erythema, pruritus, hemorrhage, and rash. No patients discontinued study treatment due to ISR.

As of 1 May 2019, ISRs have been reported in 56 of 154 (36.4%) patients dosed with gantenerumab in the WN25203 OLE study, and 45 of 154 (29.2%) patients have had recurrent ISRs. All ISRs were non-serious and mild, and the majority resolved without treatment. Overall, 3 of 56 (5.4%) patients who had an ISR received treatment, which included topical steroids and antihistamines.

As of 1 May 2019, ISRs have been reported in 86 of 225 (38.2%) patients treated with gantenerumab in the WN28745 OLE study and 58 of 225 (25.8%) patients have had recurrent ISRs. All ISRs were non-serious, with the majority being mild and resolving without treatment. Overall, 9 of 86 (10.5%) patients who had an ISR received treatment,

which included topical steroids and antihistamines. One patient (0.3%) experienced a severe event (injection-site pain after receiving a 600 mg dose via a pump, resulting in dose modification [i.e., uptitration was delayed]); this ISR resolved within 24 hours.

The Sponsor performs regular reviews of OLE Studies WN25203 and WN28745 data and, to date, has not identified any new or unexpected safety findings.

For safety data from all studies, refer to the Gantenerumab Investigator's Brochure.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Currently, approved therapies for AD focus on symptomatic approaches that target synaptic function and cognitive enhancement (Cummings 2004). However, the amyloid hypothesis suggests that overproduction of Aβ or failure to effectively clear this peptide contributes to AD (Selkoe and Hardy 2016) and that accumulation of Aβ peptides is one factor contributing to AD progression (Sun et al. 2015). Thus, the targeting of Aβ and subsequent displacement of Aβ from the brain is a rational approach to modify AD progression.

Despite compelling results in AD animal models (Wisniewski and Goñi 2014), clinical success with passive immunization targeting brain amyloid in global Phase III trials remains an unachieved goal. It has been suggested that lack of sufficient target engagement of anti-amyloid antibodies has been a factor in the failure of these Phase III studies (Cummings et al. 2016). An important advancement for therapies targeting aggregated amyloid was provided based on data from the Phase Ib PRIME study of aducanumab (Biogen) (Sevigny et al. 2016).

Aducanumab is a fully human IgG1 monoclonal antibody with similar PK and PD properties as gantenerumab that binds to aggregated target fibrillary and oligomeric forms of Aβ through microglia-mediated clearance of amyloid plaques (Sevigny et al. 2016). The results from the PRIME study showed that monthly IV injections of aducanumab for 1 year led to a dose- and time-dependent reduction of amyloid plaques in the brain. In addition, in patients with early (prodromal to mild) AD, a slowing of clinical decline, as measured on the Clinical Dementia Rating–Sum of Boxes (CDR-SOB) and MMSE scores, has also been observed providing support to the hypothesis that Aβ plaque reduction confers clinical benefit.

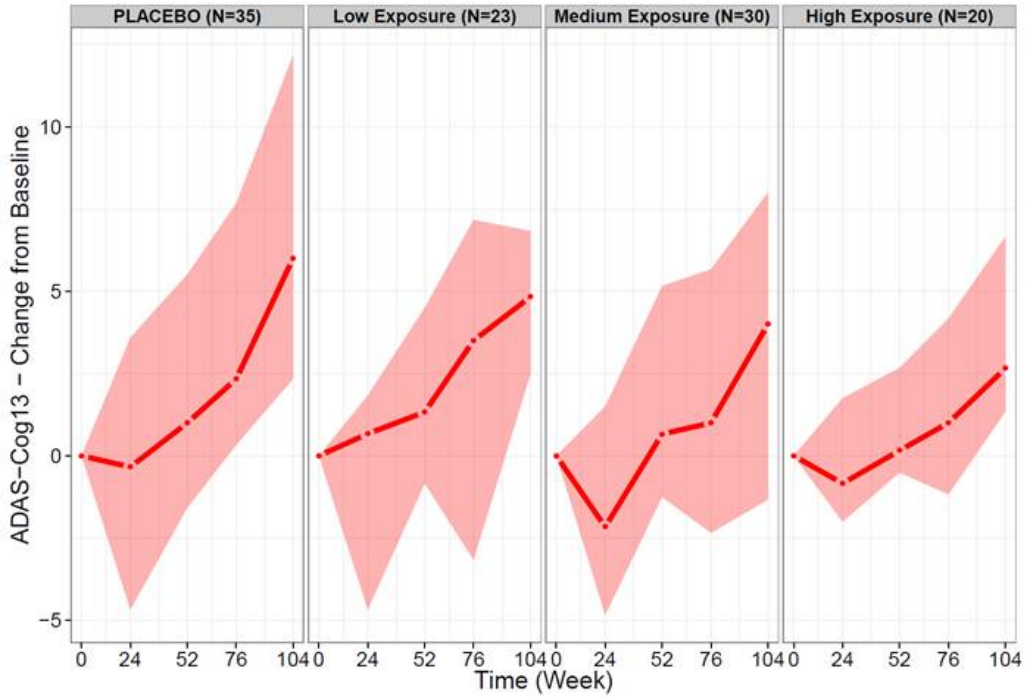
1.3.1 Study Rationale

The results of the preplanned futility analysis of data from approximately 300 patients in Study WN25203 revealed the low likelihood for trial success with the original doses studied. Indeed, no significant differences were observed on any cognitive or functional measures (i.e., CDR-SOB, MMSE, Alzheimer Disease Assessment Scale–Cognition, Subscale 13 [ADAS-Cog13], and Functional Activities Questionnaire [FAQ]) or in a subgroup analysis of baseline characteristics (demographics, cognitive, CSF biomarkers, disease severity, or *APOE* ε4 allele status). Additional post-hoc analyses

indicated that the overall rate of clinical decline was lower than expected for this study population (and with higher-than-expected proportion of “slow progressors”) and strongly suggested that the doses studied in Study WN25203 (105 and 225 mg) were subtherapeutic and that a higher gantenerumab dose may have a clinically relevant effect (Ostrowitzki et al. 2017).

Results of the post-hoc analyses of patients who were predicted to be progressors using a model derived from the Alzheimer’s Disease Neuroimaging Initiative data (Delor et al. 2013) showed a drug concentration-dependent effect on clinical decline present for the ADAS-Cog13, MMSE, and Cambridge Neuropsychological Test Automated Battery results. Figure 1 displays the effects on increasing plasma gantenerumab concentrations (three concentration groups) on ADAS-Cog13 decline over the 2-year study. Greater concentrations of gantenerumab were associated with less clinical decline.

Figure 1 ADAS-Cog13 Treatment Response by Plasma Concentration: Two-Year Completing Fast Progressors in Study WN25203

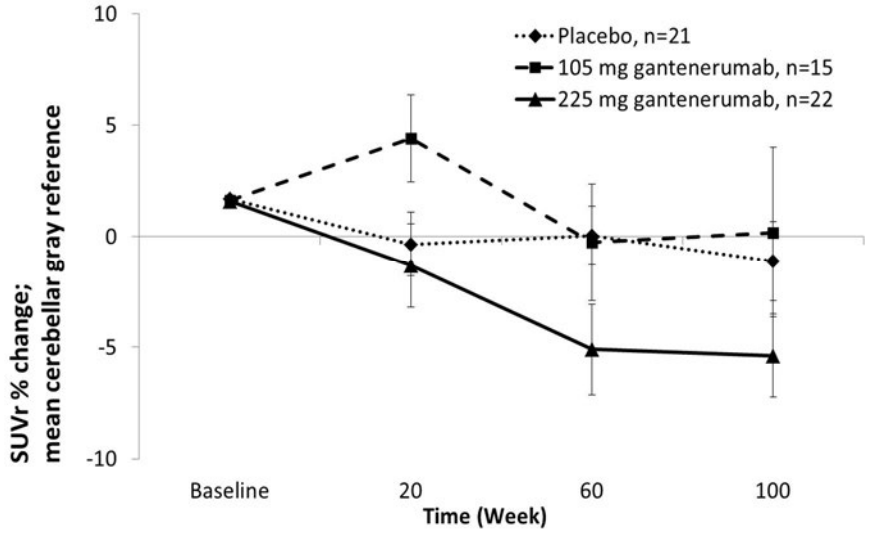


ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13.
Notes: low exposure = 1.48–5 μg/mL; medium exposure = 5–10 μg/mL; high exposure = 10–26.68 μg/mL. Line = median; shaded = 50% observations.

Furthermore, a PET substudy of Study WN25203 using [^{18}F] florbetapir confirmed a reduction in brain amyloid in gantenerumab-treated patients in a larger, less-impaired patient sample compared with Study NN19866, which had also demonstrated reduced

accumulation of brain amyloid. Time-dependent reductions in SUVr were observed in patients treated with 225 mg of gantenerumab compared with placebo using the composite cortical SUVr and reference region of mean cerebellar gray. Week 100 results showed the mean percent change from baseline in SUVr was −1.09%, 0.72%, and −4.82% in the placebo, 105-mg gantenerumab, and 225-mg gantenerumab groups, respectively (see Figure 2). A small number of patients (n=8) continued to receive 225 mg of gantenerumab for approximately 3 years (Week 156). Analysis suggested that the effect on SUVr reduction was continuous over time because SUVr reductions observed with the 225-mg dose of gantenerumab relative to placebo increased with the duration of long-term exposure, suggesting a sustained effect with continued exposure.

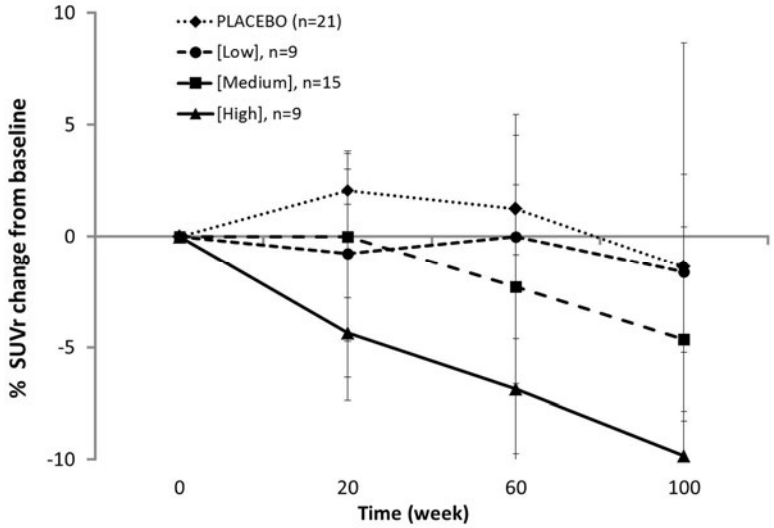
Figure 2 Mean Percent Change from Baseline in Composite Amyloid PET SUVr by Cerebellum Gray Reference: Study WN25203, PET Substudy



PET=positron emission tomography; SUVr=standardized uptake value ratio.

In Study WN25203, a concentration-based analysis of the PET results showed a clear response relationship between gantenerumab concentration in plasma and SUVr reduction, with greater mean concentrations resulting in greater amyloid clearance. As depicted in Figure 3, small changes in SUVr were present in the placebo and 1.9–5-μg/mL gantenerumab groups, whereas the higher concentration groups (5–10 μg/mL gantenerumab and 10–20.72 μg/mL gantenerumab) displayed SUVr reductions of up to 5% and 10%, respectively. These analyses indicate that higher doses may produce greater Aβ clearance that may translate into greater clinical effect.

Figure 3 Median Changes over Time in Concentration-Dependent PET SUVr by Gantenerumab Serum Concentration and Cerebellum Gray Reference: Study WN25203, PET Substudy



PET = positron emission tomography; SUVr = standardized uptake value ratio.
Note: low = 1.9–5 μg/mL; medium = 5–10 μg/mL; high = 10–20.7 μg/mL.

In addition, CSF analyses performed in Study WN25203 showed dose-dependent reductions in both CSF tau species (total tau [t-tau] and phosphorylated tau [p-tau]) in patients receiving gantenerumab compared with placebo. No change in CSF $A\beta_{42}$ was present over the 2-year period, as expected, given the mechanism of action of gantenerumab that targets fibrillar over monomeric Aβ.

Overall, these findings indicate the presence of clinical and biological effects of gantenerumab in subjects who had the highest exposure. In overall study population, results from the futility analysis of Study WN25203 indicated that the likelihood of the 225-mg dose of gantenerumab achieving a clinical effect was very low. These findings indicate that higher doses are required to achieve a clinical effect associated with the biological activity indicated by the amyloid and tau biomarker findings in Study WN25203. As a result, the decision was made to convert Studies WN25203 and WN28745 into OLE studies to give all patients the opportunity to receive higher doses of gantenerumab and to assess the safety of higher doses.

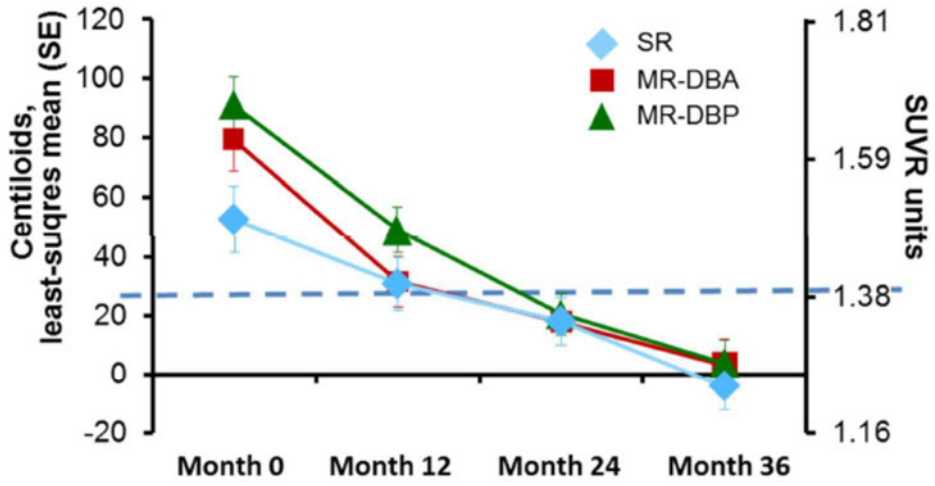
Additional support for using higher doses of gantenerumab comes from PK-PD models. Based on the established similarities between gantenerumab and aducanumab (see Section 1.3), a model characterizing the relationship between plasma drug concentration (PK) and PET response (i.e., the PD effect on amyloid load in the brain) was derived from both gantenerumab study WN25203 data and aducanumab PRIME data to determine the target dose of gantenerumab for the OLE studies (for further details see

Appendix 4). In the OLE studies, the 1200-mg dose of SC gantenerumab Q4W is predicted to achieve plasma levels comparable to 10 mg/kg of IV aducanumab Q4W and to be associated with a comparable (~20%) amyloid brain reduction, which, in the case of aducanumab, was associated with a statistically significant clinical effect after 1 year of treatment. In order to minimize the occurrence of ARIA-E while achieving the target dose within a reasonable time frame, several titration schedules have been explored in the WN25205 OLE and WN28745 OLE studies.

Gantenerumab PK-PET models of amyloid reduction have been confirmed by PET data from the OLE studies (Klein et al. 2019). There were 89 patients from the OLE studies included in an amyloid PET substudy using [^{18}F] florbetapir (Amyvid™). Of these 89 patients, 67 received follow-up scans at Week 52 of the OLE, 42 received scans at Week 104 of the OLE, and 30 received scans at Week 156 OLE, before the cutoff date of 31 Aug 2019.

Patients were divided into three analysis cohorts because of heterogeneous baseline characteristics, time off-dose before OLE dosing, and OLE titration schedules: 1) MR-DBP (Marguerite RoAD [Study WN28745] double-blind placebo subgroup), which included patients in the placebo arm of Marguerite RoAD (Study WN28745); 2) MR-DBA (Marguerite RoAD double-blind active subgroup), which included patients in the active treatment arms of WN28745; and 3) SR (Scarlet RoAD [Study WN25203] subgroup), which included a combined cohort of all patients from the Scarlet RoAD. SR patients were combined into a single cohort because all patients were off-dose for 16–19 months prior to OLE dosing. Out of 67 patients, 27 were in the MR-DBP, 21 were in the MR-DBA, and 19 were in the SR analysis cohorts. In the OLE PET substudies, a marked and consistent reduction of amyloid load in patients receiving high-dose gantenerumab was observed (see Figure 4). Mean PET centiloid reductions from baseline were –42, –48 , and –21 at Week 52; –71 , –62 , and –36 at Week 104; and –90, –75 , and –57 at Week 156 in the MR-DBP, MR-DBA, and SR analysis cohorts, respectively (see Figure 4). Amyloid reductions are consistently seen in nearly all patients of the three analysed subgroups (see Figure 5 and Figure 6).

Figure 4 Mean (SE) PET Amyloid Reductions in the OLE PET Substudies



Absolute centiloids[a]				
SR	52.7 (11.1) n = 20	30.9 (8.9) n = 19	18.2 (8.1) n = 12	**–4.1 (8.0)** n = 9
MR-DBA	79.6 (10.9) n = 21	31.7 (8.6) n = 21	18.1 (8.2) n = 11	**3.3 (9.0)** n = 6
MR-DBP	91.1 (9.6) n = 27	49.1 (7.6) n = 27	20.6 (6.9) n = 17	**4.0 (7.8)** n = 8

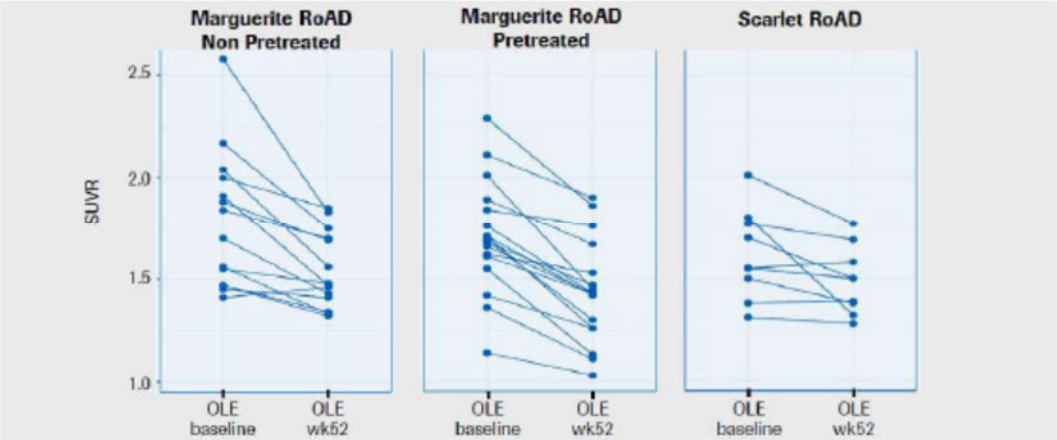
Data presented at Clinical Trials in Alzheimer's Disease (CTAD) Asia in 2019

MR-DBA = Marguerite RoAD (WN28745) pretreated subgroup; MR-DBP = Marguerite RoAD (WN28745) non-pretreated subgroup; OLE = open-label extension; PET = positron emission tomography; SE = standard error; SR = Scarlet RoAD (WN25203) subgroup; SUVR = standardized uptake value ratio.

[a] Analysed using a mixed-model for repeated measures.

The data from the OLE PET substudies showed higher reductions of amyloid plaque over a shorter time period with the 1200-mg dosing regimen of gantenerumab compared with the 105- or 225-mg dosing regimen. Mean amyloid levels were reduced by 39 centiloids by Week 52 and by 59 centiloids by Week 104, a 3.5-times greater reduction than was seen after 2 years at 225 mg.

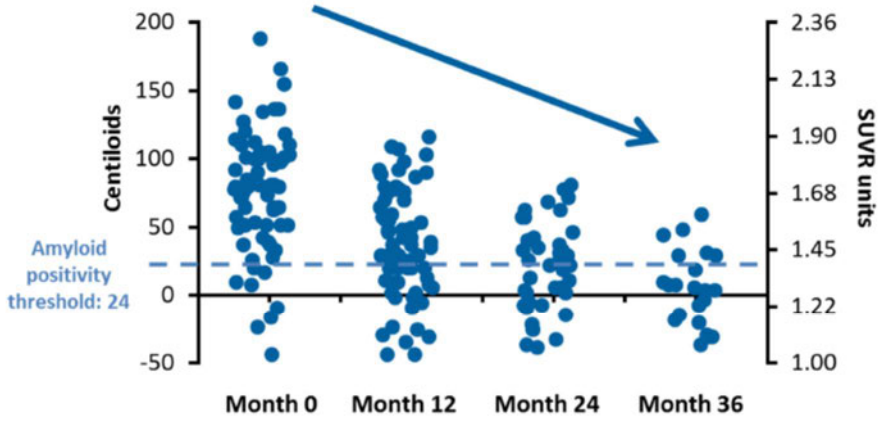
Figure 5 SUVR Reductions during the First Year of High-Dose Gantenerumab Treatment in the OLE PET Substudies



Data presented at CTAD in 2017.
OLE, open-label extension; SUVR, standardized uptake value ratio; wk, week

An important anchor for interpreting PET results is the threshold for amyloid positivity, which is the quantitative threshold that best discriminates pathologically verified absence of plaques or sparse plaques from moderate to frequent plaques. A centiloid value of 24 is generally recognized as the amyloid positivity threshold for florbetapir (Klein et al. 2019). Results in this ongoing study confirm the amyloid plaque removal component of the gantenerumab mechanism of action and show that following two years of treatment, 51% of subjects achieved below-threshold PET SUVr signals based on quantitative measures and that 74% of subjects were below threshold after three years of treatment (see Figure 6).

Figure 6 Patient-Level Amyloid Reductions Over 3 Years of Treatment in the OLE PET Substudies



Proportion of patients below amyloid positivity threshold

No. of patients	68	67	40	23
% below threshold	15%	37%	51%	74%

Data presented at CTAD Asia in 2019
SUVR, standardized uptake value ratio

1.3.2 Rationale for Dosing Strategy

As indicated in Section 1.3.1, the target dose of 1200 mg G3 material administered in the WN25203 and WN28745 OLE studies has been identified based on PK-PD modeling and simulations (details about the model are presented in Appendix 4) and is predicted to lead to an amyloid PET reduction similar to 10 mg/kg IV aducanumab Q4W. The OLE PET data have been consistent with these predictions.

In the OLE studies WN25203 and WN28745, patients were allocated to different titration schedules (two schedules in Study WN25203 and four schedules in Study WN28745) according to their *APOE* allele status and treatment arm during the double-blind period of the parent studies. These titration schedules were implemented in order to mitigate the risk of ARIA events. An ARIA-E hazard model was first developed on bapineuzemab data (Hutmacher et al. 2013). This model, which includes drug concentrations, time since first dose, and *APOE* ε4 allele status, was applied to the double-blind results in Study WN25203; the model was then tested on publicly available aducanumab data from the PRIME study and were used to predict the incidence of ARIA-E events with a high degree of accuracy, including the observed ARIA-E rate differences across *APOE* ε4 allele groups.

Recently, the ARIA-E hazard model has been updated with observations from the WN25203 and WN28745 OLE trials using higher doses of gantenerumab (see Appendix 5).

Using the validated PK-PET and ARIA-E hazard model, multiple titration options have been simulated, including separate simulations for *APOE* ε4 allele carriers and non-carriers. Two different types of titration schedules, reflecting the different risk for ARIA events between *APOE* ε4 allele carriers and non-carriers were considered. Although an *APOE* ε4 genotype–based titration regimen could permit *APOE* ε4 non-carriers to achieve the target dose more quickly, an option with a single, slower titration schedule for all patients is favored as it provides an overall lower risk for ARIA. Given the chronic and gradually progressive nature of AD, the favored option is a single, slow titration schedule for all patients because it is simpler for clinicians, less prone to error, and does not require *APOE* genotyping before the initiation of treatment.

Thus, based on the information from the WN25203 and WN28745 OLE studies, in which gantenerumab (manufactured with G3 process) up to 1200 mg Q4W was assessed and shown to be safe for APOE ε4 allele carriers and non-carriers, and based on the internally developed PK-PD models, the following dosing regimen for Study WN39658 was selected: 150 mg Q4W for 3 months, then 300 mg Q4W for 3 months, and then 600 mg Q4W for 3 months, followed by 600 mg Q2W until the end of the study. The switch to a Q2W administration schedule allows patients to decrease the number of SC administrations in the abdomen per visit.

The PK-PD models referenced above were developed based on information from the G3 material and were used to establish the initial dosing regimen for this study. As indicated previously, gantenerumab drug substance manufacturing process was optimized from G3 to G4, and a relative bioavailability study (WP40052) assessed the pharmacokinetic difference between the G3 and G4 material in humans.

The results of this relative bioavailability study (WP40052) show that the AUC_{inf} is approximately 1.18 fold and the C_{max} is approximately 1.05 fold higher after administration of G4 compared with G3. As AUC is considered the driver of the treatment effect, the conversion factor of 1.18 from the G3 to G4 material has been based on the AUC_{inf}. The association between microglial-driven removal of aggregated brain amyloid and AUC has been shown in preclinical experiments and clinical studies. In addition, as gantenerumab exhibits linear pharmacokinetics, the AUC_{inf} after single dose reflects the steady state exposure (AUC_{tau}) after multiple doses.

Based on the above rationale and the fact that gantenerumab manufactured with G4 process was safe and well tolerated, the G3 dosing regimen has been converted into the following G4 dosing regimen for the WN39658 study: 120 mg Q4W for 3 months, then 255 mg Q4W for 3 months, and then 510 mg Q4W for 3 months, followed by 510 mg Q2W until the end of the study. This schedule enables titration to target dose within 9 months (see Table 1), with predicted overall ARIA-E rate of approximately 26% based on the current ARIA-E hazard model. The low starting doses and gradual increase in dosing (i.e., slow titration schedule) are expected to reduce the risk of ARIA-E for both

APOE carriers and non-carriers. An MRI scan, confirming the absence of ARIA-E findings, will be required prior to each dose increase.

Table 1 Proposed Dose and Titration Regimen for Phase III Studies

Month	1	2	3	4	5	6	7	8	9	10
Dosing frequency	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W	Q2W
Dose (mg)	120	120	120	255	255	255	510	510	510	510

1.3.3 Risk-Mitigation Measures for ARIA Findings

ARIA is the most significant adverse event reported in therapies against aggregated forms of Aβ. These findings appear to be dose, time, and *APOE* ε4 allele dependent (Piazza and Winblad 2016).

The mechanism underlying the development of ARIA-E and ARIA-H during anti-amyloid treatment is unknown. Because antibodies target removal of Aβ from both the parenchyma and cerebral vasculature, vessels with preexisting amyloid vascular pathology might become transiently more susceptible to leakage of vascular contents. This pathology results in ARIA-E if the leakage consists of proteinaceous fluid and in ARIA-H if the leakage consists of blood products (Sperling et al. 2012).

Thus, an anti-Aβ therapy that effectively maintains vascular β-amyloid clearance would allow vascular remodeling and may, with time, decrease the risk of such extravasation events (Sperling et al. 2012). This is consistent with experience in previous and ongoing studies and with reported data from the long-term extension study of aducanumab treatment (Viglietta et al. 2016).

Previous and ongoing studies with gantenerumab showed that ARIAs are manageable with MRI monitoring and dose intervention algorithms (i.e., temporary study drug interruption or temporary suspension of uptitration) and that these events are mostly asymptomatic. Data from the long-term extension of the PRIME study (aducanumab) suggested also that a titration up to 10 mg/kg (predicted to be comparable to 1200 mg of SC Q4W G3 gantenerumab (or 510 mg of SC Q2W G4 gantenerumab) per the PK-PD model (see Appendix 4) may reduce the incidence of ARIA-E compared with higher fixed dosing (Viglietta et al. 2016).

In Study WN39658, imaging-related criteria are used to exclude patients with clinically important cerebral vascular disease at baseline, as well as ARIA-related lesions. A slow titration schedule will be implemented to reach the target dose, and MRI monitoring will be conducted during the study at regular intervals (see Appendix 1 for the schedule of activities for the uptitration and MRI schedules). An MRI scan documenting the absence of ARIA-E findings will be required prior to each dose increase. If ARIA findings occur, more intense MRI monitoring, dose adjustments, temporary dose holding, or permanent

discontinuation will be implemented according to an ARIA-related dose-adjustment plan, described in Section 5.1.2. Safety findings (including unblinded individual patient and aggregate data) will be reviewed on a regular basis by the iDMC.

1.3.4 Risk to Participants without Alzheimer's Disease Pathology

Owing to the rigorous screening procedures in this study, including measurement of the CSF tau to $A\beta_{42}$ ratio and/or amyloid PET scan, it is anticipated that only participants with AD pathology will be enrolled. In the event that a participant without amyloid pathology is enrolled, no additional risk is expected. However, such participants may still experience side effects related to administration of gantenerumab (e.g., ISRs and development of anti-drug antibodies [ADAs]).

1.3.5 Overall Benefit–Risk Summary

Overall, the benefit–risk assessment of gantenerumab is based on the following:

- Gantenerumab has shown evidence of reducing amyloid plaques (i.e., observed evidence of brain amyloid reduction) and, thus, shows potential benefit in slowing the progression of AD.
- Findings from the WN25203 and aducanumab PRIME studies provide additional support for the hypothesis that anti-amyloid treatment may be associated with a beneficial clinical effect.
- Results from the double-blind portions, as well as from the OLEs of studies WN25203 and WN28745, showed that ARIA findings are mostly asymptomatic, non-serious, of mild severity, and do not require permanent cessation of treatment. ARIAs are manageable with MRI monitoring and dose intervention algorithms, as detailed in Section 5.1.2.
- No new safety signal has been identified in the data from the ongoing OLE studies with doses of up to 1200 mg Q4W G3 material. These data support the administration of the target dose of 510 mg Q2W G4 material to both ApoE ε4 carriers and non-carriers in the WN39658 study.
- *The benefit risk ratio of conducting the WN39658 study during the pandemic remains unchanged. This is supported by the preclinical and clinical data collected through the development program of gantenerumab where there has been no indication that gantenerumab administration compromised the immune system or made individuals more susceptible to infections.*
  Thus, there are no data or biological rationale suggesting that Gantenerumab administration could increase the risk of infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or more severe coronavirus disease 2019 (COVID-19) outcomes.
  Participating in study visits at the investigational sites may however increase the risk of exposure to SARS-COV-2, therefore, whenever appropriate, the Sponsor allows the possibility to perform home visits by adequately trained health care professionals. All necessary precautions will be taken to protect the health of the study participants and minimize the risk of exposure. As such the PI, in addition to

all appropriate study staff that come into contact with the study participants, will wear personal protective equipment during the visit as per local requirements.

Thus, the anticipated benefit–risk profile of gantenerumab supports clinical trials with higher doses in the population with early (prodromal to mild) AD.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of gantenerumab compared with placebo in participants with early (prodromal to mild) AD. Specific objectives and corresponding endpoints for the study are outlined in Table 2 for the double-blind treatment period and in Table 3 for the OLE period.

Table 2 Objectives and Corresponding Endpoints for the Double-Blind Treatment Period

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of gantenerumab administered by SC injection compared with placebo	The change from baseline (Day 1) to Week 116 [a] in global outcome, as measured by the CDR-SOB
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo on cognition and function	The change from baseline to Week 116 [a] in cognition and/or function as measured by: • MMSE total score • ADAS-Cog11 and ADAS-Cog13 • Verbal Fluency Task • Coding • FAQ • ADCS-ADL total score and instrumental score
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo	The change from baseline to Week 116 [a], in the following: • Clinically evident decline as *measured using the CDR* • Severity, as assessed by the CDR Global Score • Dependence level, as derived from the ADCS-ADL score • Health-related quality of life, as assessed by the QoL-AD scale • Behavioral and neuropsychiatric symptoms of AD, as measured by the NPI-Q • Study partner burden, as assessed by the ZCI-AD scale • Elements of resource utilization, as assessed by the RUD-Lite • Health outcomes in participant and study partner, as measured by EQ-5D questionnaire

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

[a] If the double-blind treatment period is extended by a total of 24 weeks, the endpoints will be based on change from baseline to Week 128.

Table 2 Objectives and Corresponding Endpoints for the Double-Blind Treatment Period (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of gantenerumab compared with placebo	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Presence of ADAs during the study relative to the presence of ADAs at baseline (in active treatment group only)
Pharmacodynamic Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo in participants with early (prodromal to mild) Alzheimer's disease	• Change from baseline *to Week 116* in brain amyloid load, as measured by amyloid PET scan in a subset of participants • Change from baseline *to Week 116* in brain tau load, as measured by tau PET scan in a subset of participants • Change from baseline *to Week 116* in cerebral spinal fluid markers of disease in a subset of participants, including, but not limited to, total tau, and phosphorylated tau
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo in participants with early (prodromal to mild) Alzheimer's disease	• Change over time in plasma *and other CSF* biomarkers (see Section 4.5.6.2) • Change from baseline to Week 116 [a] in functional brain connectivity, as measured by resting-state functional MRI (where available) • Change from baseline to Week 116 [a] in integrity of white matter, as measured by DTI-MRI (where available) • *MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all participants*
Exploratory **Pharmacokinetic Objective**	**Corresponding Endpoint**
• To characterize the PK profile of gantenerumab	• Plasma concentration of gantenerumab (administered subcutaneously) at specified timepoints

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

[a] If the double-blind treatment period is extended by 24 weeks, the final endpoints will be based on change from baseline to Week 128.

Table 3 Objectives and Corresponding Endpoints for the Open-Label Extension Period

Safety Objective	Corresponding Endpoints
• To evaluate the long-term safety and tolerability of SC gantenerumab in participants with early AD	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Presence of ADAs during the study relative to the presence of ADAs at baseline
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To assess the long-term efficacy of SC gantenerumab in participants with early AD	• The change in cognition, function and other outcomes over time, as measured by: • CDR • MMSE • ADAS-Cog11 and ADAS-Cog13 • Verbal Fluency Task • Coding • FAQ • ADCS-ADL • Health-related quality of life, as assessed by the QoL-AD scale • Behavioral and neuropsychiatric symptoms of AD, as measured by the NPI-Q • Study partner burden, as assessed by the ZCI-AD scale • Elements of resource utilization, as assessed by the RUD-Lite • Health outcomes in participant and study partner, as measured by EQ-5D questionnaire

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

Table 3 Objectives and Corresponding Endpoints for the Open-Label Extension Period (cont.)

Exploratory Pharmacodynamic Biomarker Objective	Corresponding Endpoints
• To evaluate the long-term effect of SC gantenerumab in participants with early AD	• Brain amyloid load over time, as measured by amyloid PET scan in a subset of participants • Brain tau load over time, as measured by tau PET scan in a subset of participants • Cerebral spinal fluid markers of disease over time in a subset of participants, including, but not limited to, $A\beta_{1-42}$, total tau, and phosphorylated tau • MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, functional brain connectivity, integrity of white matter in all participants • Plasma markers over time *in all participants*

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of gantenerumab in participants with early (prodromal to mild) AD.

The planned number of participants for the global enrollment phase for the study is approximately 1016 participants randomized in a 1:1 ratio to receive gantenerumab and placebo (508 participants randomized to gantenerumab and 508 randomized to placebo) (see Section 6.1). To maintain a balanced number of participants enrolled in each treatment arm and to ensure that the arms are comparable, randomization will be stratified by stage of disease (prodromal AD vs. mild AD), APOE allele status (presence vs. absence of the ε4 allele), use of AD medication (presence vs. absent), geographic region (Western Europe and Australia vs. Rest of the World vs. North America) and participation in longitudinal amyloid and tau PET substudies. Approximately 175 centers in approximately 15 countries worldwide will participate in this study.

Participants will be selected on the basis of clinical diagnosis of probable AD (according to the National Institute on Aging/Alzheimer's Association [NIA/AA] diagnostic criteria and guidelines for AD; see Appendix 2) (McKhann et al. 2011) or prodromal AD (according to the NIA/AA diagnostic criteria and guidelines for MCI due to AD; see Appendix 3) (Albert et al. 2011). The aim of the study is to recruit approximately 50% of the participants with prodromal AD.

Eligible participants will be 50–90 years old, inclusive, must show evidence of β-amyloid pathology as indicated by the CSF tau to Aβ42 ratio (CSF-enrolled participants) or positive amyloid PET scan by visual read (PET-enrolled participants), and meet eligibility criteria as detailed in Section 4.1.

The study will consist of a screening period of up to 12 weeks in length following the signing of informed consent. Sites also have the option to prescreen participants on the FCSRT and MMSE. Participants must sign a separate Informed Consent Form before administration of these tests if used for prescreening. If the results confirm a participant's eligibility, then the FCSRT and MMSE will not have to be completed again during the screening period as long as the test has been done within 12 weeks prior the baseline.

Eligible participants will then undergo baseline visit assessments (Day 1) prior to receiving the first dose of blinded study drug (gantenerumab or placebo). Participants will continue in the double-blind treatment period.

Due to the global impact of the COVID-19 pandemic and the resulting disruption in study drug administration, the duration of the double-blind treatment period will be extended by 12 weeks, with the possibility of an additional 12-week extension (for a total of 24 weeks). This may result in the following scenarios:

- Scenario 1: Participants who are enrolled and active in the double-blind treatment period after implementation of Protocol Version 4 will have the double-blind treatment period extended by 12 weeks, with the final efficacy and safety visit at Week 116 (Appendix 1).
- Scenario 2: If the COVID-19 pandemic results in greater than anticipated disruptions to study drug administration, then the Sponsor has the option to extend the double-blind treatment period by an additional 12 weeks, with the final efficacy and safety visit at Week 128 (Appendix 1). This extension will be mandatory for all patients who are active in the double-blind treatment period at the time that the extension decision is implemented.

Participants who have already had the last study drug administration at Week 102 and their final efficacy and safety visit at Week 104 and who have completed the double-blind treatment period prior to implementation of *the study extension by 12 weeks*, will continue into the OLE of either the WN39658 study or the WN42171 study. Alternatively, they will continue into the safety follow-up period.

For participants who enroll or who are active in the double-blind treatment period at the time of implementation of *the study extension by 12 weeks*, visits and study drug administration will occur Q4W until participants reach the target dose, which will be 510 mg Q2W. After the last dose of study drug (Week 114 for scenario 1 and Week 126 for scenario 2, if applicable), final efficacy and safety assessments will be performed 2 weeks later (at Week 116 for scenario 1 and at Week 128 for scenario 2, if applicable). Participants may then enroll in an OLE study if they are eligible (either in the OLE part of this study or in the WN42171 study) or have safety follow-up visits 14 and 50 weeks after the last dose for safety and limited efficacy assessments.

All participants who prematurely discontinue treatment will continue participating in the study and will be asked to return for collection of safety and limited efficacy data (see Section 4.7.1).

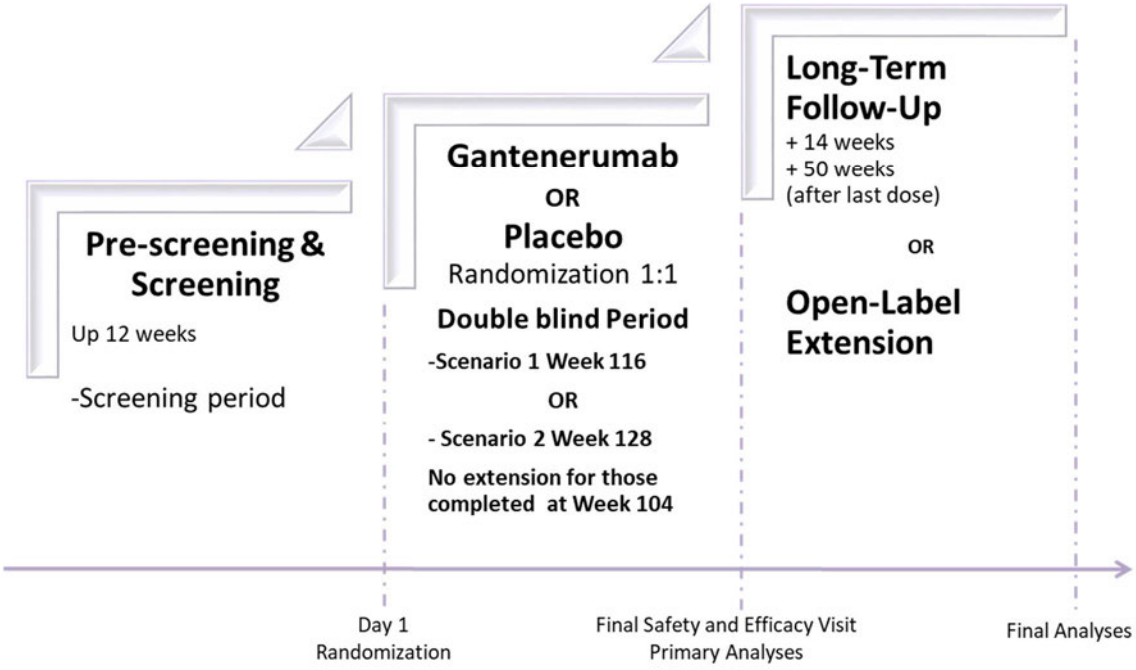
Participants will undergo brain MRI examinations for safety monitoring and longitudinal changes in brain structure. MRI scans will be read by a central MRI reader (for more details regarding imaging-related criteria, see Section 4.1.2.2). Participants will also undergo standard tests to monitor safety (blood tests, ECG), as well as the Columbia–Suicide Severity Rating Scale (C-SSRS) to monitor for suicidality, tests for cognition, function, and QoL status. Blood samples for the assessment of PK samples, PD biomarkers, and ADA will be obtained from all participants.

The incidence and nature of adverse events, serious adverse events, ARIA-E, ARIA-H, ISRs, adverse events of special interest, ECGs, and laboratory abnormalities will be assessed on a regular basis by an unblinded iDMC.

An overview of the study design is provided in Figure 7. The schedule of activities is provided in Appendix 1.

Once the double-blind treatment period is completed, participants who consent and are eligible may opt to participate in an OLE. If the stand-alone open-label study (Study WN42171) is not open for enrollment at the time that a participant completes the double-blind treatment period of this study, then the participant will follow the OLE procedures described in this study (Section 4.3.2.2 and Appendix 1). These participants will then transition to Study WN42171 after they have completed the entire schedule of activities in the OLE of this study and the protocol for Study WN42171 is available and approved as per local requirements. If Study WN42171 is open for enrollment at the time that a participant completes the double-blind treatment period of this study, then the participant will enroll directly in Study WN42171 and not in the OLE portion of this protocol. *The OLE of Study WN39658 is not applicable in countries that cannot run Study WN42171.*

Figure 7 Overall Study Design



W=week

The study consists of three distinct periods:

- Screening (including an optional pre-screening): The screening period may last up to 12 weeks for each eligible participant.
- Double-blind treatment period: After screening, participants who meet all eligibility criteria will be randomly assigned to one of two arms (gantenerumab or placebo) in a 1:1 ratio. Following baseline assessments, each participant will receive a minimum of nine SC Q4W administrations of study drug (uptitration period), followed by up to 40 administrations of study drug in the double-blind treatment period in scenario 1 or up to 46 administrations in scenario 2, if applicable. The last dose of study drug will be administered at Week 114 in scenario 1 and at Week 126 in scenario 2, if applicable. At the end of the double-blind treatment period, 2 weeks after the last dose, all participants will undergo the final safety and efficacy study visit. Participants who have already completed the double-blind treatment period prior to implementation of *the study extension by 12 weeks* will have received 34 SC Q2W administrations of study drug during the double-blind treatment period. The last dose will be administered at Week 102, and their final efficacy and safety visit will be at Week 104.
- Post–double-blind treatment period: After the final efficacy and safety study visit, all participants will be asked to come back for the long-term follow-up visits or to continue in the OLE.

  Long-term follow-up: Long-term follow-up will consist of a 50-week follow-up period with evaluations at Weeks 14 and 50 after completion of study drug administration. Participants who withdraw early during the double-blind treatment period or during the OLE period are also asked to complete the long-term follow-up visits.

  OLE: All eligible participants will have the opportunity to enter an OLE study.

  – Eligible participants who enrolled early in the WN39658 study may start the OLE as detailed in Appendix 1, Table 5, and Table 6, and will then transition to the open-label study WN42171 (details will be provided in protocol WN42171). Participants who terminated the WN39658 OLE early will be asked to come back for long-term follow-up visits.
  – If the WN42171 protocol is available and approved by local authorities, the eligible participants will directly be enrolled in the open-label study WN42171.

For the schedule of activities at each visit, see Appendix 1.

China Enrollment Plan

Based on historical data, participant recruitment is expected to take longer in China; therefore, a specific China enrollment plan has been established. Thus, if at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA during the global enrollment phase, additional participants may be enrolled in a China extension to ensure a total enrollment that is sufficient to support

registration in China. All participants enrolled at NMPA-recognized sites in the global enrollment phase will be included in the primary analysis. All participants enrolled at NMPA-recognized sites in the global enrollment phase and the China extension phases will be included in a China-specific analysis. Details will be provided in the SAP.

3.1.2 Substudies

The substudies associated with Study WN39658 will be described in separate protocols, and participants consenting to enroll in these substudies will be asked to sign the associated Informed Consent Forms.

To date, there are two substudies associated with Study WN39658: a longitudinal Amyloid PET substudy and a longitudinal Tau PET substudy. The amyloid- and tau-PET assessments will allow a longitudinal evaluation of the effect of gantenerumab on brain amyloid deposition as measured by florbetaben or flutemetamol PET radioligands and tau burden as measured by [^{18}F] GTP1 (an investigational radioligand for in vivo imaging of tau protein aggregates) in participants with early AD. Details of any interim analyses relating to the substudies will *also* be described in the substudy protocols.

The PET data that are collected are expected to help in understanding the effects of gantenerumab on amyloid and tau pathology over time as well as the relationship between change in florbetaben/flutemetamol/[^{18}F] GTP1-PET and changes in other endpoints in the study WN39658.

3.1.3 Data Monitoring Committee

The iDMC will evaluate participant safety and efficacy on a regular basis. In addition to the data defined in the iDMC Charter (e.g., the incidence and nature of adverse events, serious adverse events, adverse events of special interest, ARIA-E, ARIA-H, and ISRs), the iDMC will review all necessary cumulative data at regular intervals during the study, including efficacy when needed. It is anticipated that these assessments will occur approximately every 3 months. At the time of each review, the iDMC will make appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, the treatment regimen should be modified, the protocol should be amended, enrollment should be held pending further safety evaluations). The iDMC will also evaluate planned or unplanned interim analyses for efficacy or futility (see Section 6.7.1).

Decisions will be made in consideration of the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities are detailed in the iDMC Charter.

Final decisions will rest with the Sponsor.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for safety analyses or safety follow-up is received for the last participant, whichever occurs later.

The study will consist of a screening period of up to 12 weeks (including the optional prescreening period) for each eligible participant who signs the Informed Consent Form and agrees to participate, followed by a double-blind treatment period of study drug treatment plus a visit 2 weeks after the last dose. The duration of the double-blind treatment period is extended by 12 weeks (116 weeks in total in scenario 1). In case scenario 2 is implemented, the double-blind treatment period will be extended by 24 weeks (128 weeks in total in scenario 2, if applicable). For participants not entering the OLE period, this will be followed by the post–double-blind treatment period of two follow-up visits at 14 and 50 weeks after the last dose. Thus, for a participant not entering the OLE period, the maximum length of study is approximately 176 weeks in scenario 1 or 188 weeks in scenario 2 (if applicable).

For participants entering the OLE period, the extension will consist of an open-label period of at least 35 weeks. If a participant is ready to be uptitrated to the target dose and if the safety MRI allows, the participant will then be transitioned to the WN42171 open-label study. If there is an ongoing ARIA-E, the participant will remain in Study WN39658 until the ARIA-E resolves and the participant is ready to be uptitrated to the target dose. In case the dosing is temporarily interrupted for any other reason, the participant will be kept in the WN39658 study until they are ready to be uptitrated to the target dose. Participants who are not willing to transition to the WN42171 open-label study after OLE Week 35 will be asked to come back for two follow-up visits at 14 and 50 weeks after the last dose (OLE Follow Up 1 and Follow Up 2, respectively).

3.3 RATIONALE FOR STUDY DESIGN

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of gantenerumab in participants with early (prodromal to mild) AD, increased amyloid burden (defined according to CSF or PET criteria), and clinical symptoms.

3.3.1 Rationale for Participant Population

As the accumulation of Aβ brain amyloid begins before the onset of AD dementia, it is reasonable to postulate that the benefit of anti-amyloid therapy may be greater if initiated at an early stage of the disease. For this reason, Roche has focused clinical development of gantenerumab on early (prodromal to mild) AD.

Participants in this study are required to meet standard research criteria for mild AD (according to the NIA/AA research criteria and guidelines for AD; see Appendix 2) or prodromal AD (according to the NIA/AA research criteria and guidelines for MCI due to

AD; see Appendix 3). Note that the terms "prodromal AD" and "MCI due to AD" are considered to refer to the same population in this study and are defined according to NIA/AA research criteria and guidelines for MCI due to AD. Thus, participants with prodromal AD will present with documented objective evidence of deficit in one cognitive domain. Participants with mild AD must present with documented deficits in at least two cognitive domains and evidence of functional decline. Overall, the population will have an MMSE between 22 and 30 (inclusive) points and a CDR global score (CDR-GS) of 0.5 or 1.0. The MMSE score provides evidence of no more than mild disease severity and the CDR-GS score indicates that the participants have prodromal AD or cognitive and functional deficits consistent with mild AD. The aim of the study is to recruit approximately 50% of the participants with prodromal AD.

Gantenerumab is an antibody that targets Aβ. Thus, the study population should have documented evidence of amyloid pathology. This participant selection approach is consistent with the NIA/AA research diagnostic criteria and guidelines for AD as well as with the Qualification Opinion from the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use on the use of CSF biomarkers for enrichment of trials in mild to moderate AD dementia (2012), and the U.S. Food and Drug Administration (FDA's) draft guidance for early AD (2013). Although the FDA's guidance refers to the early stage of AD in which individuals present with clinical MCI, biomarkers of amyloid pathology are expected to add value to participant selection in mild AD studies, especially for anti-amyloid treatments (McKhann et al. 2011; Dubois et al. 2014, 2016). Biomarker enrichment is important for anti-amyloid therapy clinical trials because some results of early trials have demonstrated that approximately 20% participants who are enrolled in trials based on a clinical diagnosis of AD alone may not have underlying amyloid pathology as assessed by amyloid PET (Doody et al. 2014; Salloway et al. 2014).

For enrollment in this study, biomarker evidence of β-amyloid deposition will be assessed either by a centralized visual assessment of PET amyloid imaging, using one of the three following amyloid PET imaging tracers (Vizamyl™, Neuraceq™, and Amyvid™ according to country and site availability) or by the CSF tau to $A\beta_{42}$ ratio (using a prespecified cutoff and the Roche Diagnostics Elecsys immunoassay).

Both methods (CSF and PET) are established approaches to identify Aβ accumulation in the brain in vivo (Pannee et al. 2016; Vos et al. 2016) and both have been used in research and in clinical practice. There is also emerging evidence that indicates consistency between PET amyloid imaging and CSF biomarkers. Indeed, in biomarker research studies, concordance between amyloid PET and the combination of CSF $A\beta_{1-42}$ with t-tau has been shown to be very high with properly controlled CSF methodologies (EMA 2012).

To enrich for participants who are more likely to decline over the 2-year trial, all participants have to demonstrate amnestic deficits as measured by the FCSRT's total

free recall score and cueing index (Sarazin et al. 2007). The use of the FCSRT to support a hippocampal-related memory deficit (Buschke 1984; Grober and Buschke 1987) has been recommended by the International Working Group (IWG-1; Dubois et al. 2007, 2010). Indeed, the core clinical symptom of AD is significant and progressive episodic memory impairment. Memory impairments because of AD are known to be hippocampal dependent and are thought to be characterized by a deficit in recall, which is often not recovered with cueing.

The FCSRT is a cued recall test that uses controlled encoding to ensure that impaired recall and cueing results are due to memory impairment and are not a failure at encoding (e.g., by means of attentional impairment). The FCSRT has demonstrated high sensitivity and specificity in differentiating participants with AD from both healthy controls and participants with other forms of dementia (Grober et al. 2008, 2010). More recently, the choice of the FCSRT as a valid clinical marker for typical prodromal AD (amnestic MCI) has been endorsed by the IWG-2 (Dubois et al. 2014) and is supported by studies showing that this test is a good tool to use for predicting progression to AD for participants with prodromal AD (Mura et al. 2014; Lemos et al. 2015). In addition, data generated from Roche datasets showed that a cueing index of ≤ 0.67 is a good predictor of cognitive decline. Therefore, the FCSRT cueing index of ≤ 0.67 and a free recall score of ≤ 27 have been selected as inclusion criteria for this study. The cueing index measures the ability of a participant to benefit from being reminded using specific cue words to recall the target word. To prevent participants who have a high free recall and who do not appear to benefit from being reminded from being included simply because of apparent low cueing index, a free recall score of ≤ 27 will also be required.
The FCSRT index is consistent with that published by Sarazin et al. (2007) and Auriacombe et al. (2010).

3.3.2 Rationale for Use of a Placebo Control Group

Study WN39658 is a placebo-controlled trial in which participants will be eligible for study participation whether or not participants are receiving standard-of-care medications for AD (i.e., acetylcholinesterase inhibitors, memantine, and/or medical food supplements). Given that there are currently no approved disease-modifying compounds that could serve as an active control, participants will be randomized to receive gantenerumab or placebo on top of background therapies.

3.3.3 Rationale for Gantenerumab Dosage and Titration Schedule

In the OLE studies (WN28745 and WN25203), different titration schedules (based on prior double-blind treatment exposure and *APOE* $\varepsilon 4$ status) have been utilized to enable all participants to reach a target dose of 1200 mg SC Q4W while managing the risk for ARIA with MRI monitoring and dose intervention algorithms. In addition, data from the OLE studies support treatment at a low starting dose with a gradual increase in dosing (i.e., slow titration schedule) to reach target dose and to reduce the risk of ARIA findings.

As presented in Section 1.3.2, a target dose of 510 mg Q2W along with a titration schedule with a low starting dose and gradual increase in dosing (i.e., slow titration schedule) that is expected to reduce the risk of ARIA-E for both APOE carriers and non-carriers have been identified for the current study.

Therefore, all participants in Study WN39658 (regardless of APOE ε4 status) will receive 120 mg of SC gantenerumab Q4W for 3 months, 255 mg SC Q4W for 3 months, and 510 mg SC Q4W for 3 months prior to reaching target dose of 510 mg Q2W after 9 months of titration (see Section 1.3.2 for additional details about the conversion of G3 dosing regimen to G4 dosing regimen). Based on the model predictions (see Appendix 5), the overall ARIA-E rate is expected to be approximately 26%. An MRI scan, confirming the absence of ARIA-E findings, will be required prior to each dose increase.

3.3.4 Rationale for Treatment Duration

3.3.4.1 Rationale for Double-Blind Treatment Duration

According to the EMA's guidance on medicinal products for the treatment of AD and other dementias (EMA 2018) controlled clinical trials aimed at demonstrating short-term improvement in mild to moderate AD should last at least 6 months. In order to establish an effect on disease progression, a distinction between symptomatic and disease-modifying effects of a medicinal product has to be made. In addition to demonstrating a relationship between clinical outcomes and an effect on biomarkers of disease pathology, clinical improvement must be shown over a time period that is relevant to the proposed mechanism of action and the expected natural progression rate of the disease. In AD research, long-term placebo-controlled trials are needed in order to allow time for an efficacious therapy to reverse a longstanding disease process as well as to allow time for a sufficient number of placebo-treated participants to progress. Eighteen months was assumed to be of sufficient length in some recently completed Phase III studies of anti-Aβ antibodies (EMA 2018). In prodromal disease stages, even longer studies may be necessary. In addition, placebo decline is expected to be greater in longer studies; this greater decline allows an increased potential to demonstrate a treatment effect.

A 2-year treatment duration was selected as the most appropriate duration for assessment of the primary endpoint. The duration was based on the mechanism of action of gantenerumab, which is expected to delay and reduce AD progression over time compared with control. As 9-month titration period to reach the target dose is needed, a 2-year treatment period may also be appropriate for the assessment of the primary endpoint. To capture an earlier signal of efficacy, should it be present, assessments relevant to the study objectives will also be obtained at 6, 12, and 18 months.

Measures taken globally during the COVID-19 pandemic are expected to affect the protocol-specified administration of study drug. At the date of writing Protocol Version 4,

it is expected that participants will miss an average of 8 weeks of study drug administration over the course of the original 2-year study. This has the potential to decrease the power of the study (see Section 6.1 for details). To mitigate the impact of missed administrations, the double-blind treatment period is being extended by 12 weeks. The continuing impact of the COVID-19 pandemic on study procedures will be closely monitored. If the COVID-19 pandemic results in greater than anticipated disruptions to study drug administration, the Sponsor may further extend the double-blind treatment period by an additional 12 weeks (24 weeks in total).

3.3.4.2 Rationale for OLE Treatment Duration

An open-label treatment duration of at least 9 months has been selected to offer the first participants randomized in Study WN39658 open-label gantenerumab until the protocol WN42171 open-label study is available and approved. A duration of 9 months corresponds to the uptitration period; thus, when these first participants reach the target dose, they will be able to start the WN42171 open-label study at the target dose (i.e. 510 mg Q2W).

3.3.5 Rationale for Long-Term Follow-Up

The primary objective of the long-term follow-up is to estimate the long-term safety of gantenerumab over an extended period of time. Study assessments performed 14 and 50 weeks after the last dose of study drug will be used to evaluate the effects of treatment on both efficacy and safety parameters over an extended period after study drug discontinuation. Assessments will be conducted for all participants who discontinue treatment during the double-blind treatment period, during the OLE period, or who complete the double-blind period but do not enter the OLE period or who complete the OLE period but do not enter in the WN42171 open-label study. Assessments will also allow for the exploration of the long-term effects with declining drug exposure.

3.3.5.1 Rationale for Duration of Study Follow-Up (14 Weeks)

The primary purpose of the 14-week follow-up visit (i.e., 14 weeks after the last dose) is to evaluate the long-term safety of gantenerumab. The apparent terminal half-life of gantenerumab is in the order of 24 days, and gantenerumab is cleared from plasma after approximately 16 weeks (approximately 5 half-lives). Therefore, safety assessments performed 14 weeks after the last dose are considered sufficient to evaluate residual effects on peripheral safety outcomes. In addition, efficacy assessments at the follow-up visit may support an enduring effect of gantenerumab after treatment is stopped.

3.3.5.2 Rationale for Long-Term Follow-Up (50 Weeks)

Assessments performed 50 weeks after the last dose will be used to evaluate the long-term effects of study drug on both efficacy and safety parameters. The assessments will allow for the exploration of the long-term effects of study drug given the expected level of decline over this period. Participants will not be restricted from starting new treatment and therefore, the analysis will be considered exploratory.

3.3.6 Rationale for Primary Outcome Measure: Clinical Dementia Rating–Sum of Boxes

AD is considered a continuous disease that passes through consecutive stages without discrete transition points. Thus, the use of a single endpoint across both subpopulations of early (prodromal to mild) AD is consistent with the current understanding of AD.

Showing the benefit of new therapies for participants in the early stages of AD is challenging, owing to the lack of sensitive assessment tools. Use of the CDR-SOB as the primary outcome measure for studies of early (prodromal to mild) AD enables simultaneous demonstration of benefit on primary symptoms and clinical relevance (Aisen 2009, 2011), while also ensuring use of a clinical outcome assessment with adequate measurement properties (FDA 2013).

The Washington University CDR is a global assessment instrument that yields global scores (GS) and SOB scores. The CDR is derived from a semi-structured interview with the participant and an appropriate informant, and it rates impairment in six categories (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) on a 5-point scale for which 0 = no impairment, 0.5 = questionable impairment, and 1, 2, and 3 = mild, moderate, and severe impairment, respectively. From the six individual category ratings, or box scores, the CDR-GS is established by clinical scoring rules, for which CDR 0 = no dementia and CDR 0.5, 1, 2, or 3 = questionable, mild, moderate, or severe dementia, respectively (Morris 1993). The CDR-SOB score is a detailed quantitative general index that provides more information than the CDR-GS in participants with early (prodromal to mild) dementia (Coley et al. 2011; Cedarbaum et al. 2013). In particular, the CDR-SOB has been proposed for use in longitudinal assessment of dementia and is widely used in AD studies as a global measure of disease progression (Williams et al. 2013). The FDA's draft guidance for developing drugs for the early stages of disease suggests that a composite scale, validated in participants with early-stage disease that includes both cognition and function as a single primary efficacy outcome measure, is appropriate. The CDR-SOB is an example of a measure that fulfills these criteria (FDA 2013) and is now being utilized as the sole primary endpoint in several studies utilizing participant populations with early (prodromal to mild) AD, including the CREAD (crenezumab), PRIME (aducanumab), ENGAGE/EMERGE (aducanumab), and Clarity AD (BAN2401) studies.

3.3.7 Rationale for Pharmacokinetic Sampling

A sparse sampling schedule is being utilized to minimize participant burden and yet provide an adequate characterization of the population PK profile of gantenerumab. The PK data may be combined with available data from other gantenerumab studies and may be used to assess exposure–response relationships for relevant imaging, CSF, plasma PD biomarkers, ECGs, and efficacy and safety outcomes in participants with early (prodromal to mild) AD, as appropriate.

3.3.8 Rationale for Biomarker Assessments

The following biomarker assessments described in Sections 3.3.8.1 (CSF), 3.3.8.2 (PET imaging), and 3.3.8.3 (brain volumetry, connectivity, and fiber tract integrity) will be used to investigate the effect of gantenerumab on the underlying pathology of AD in the participant population.

3.3.8.1 Cerebral Spinal Fluid Biomarkers

Amyloid plaque deposition, neurofibrillary tangle formation, and neuronal degeneration are known pathologic features of AD. Decreased CSF $A\beta_{1-42}$ and elevated CSF t-tau and p-tau are considered a biochemical signature of AD. Accumulating evidence suggests that low CSF $A\beta_{1-42}$ reflects underlying amyloid plaque pathology, whereas increased t-tau and p-tau levels may be reflective of neurodegeneration and/or tau pathology. Amyloid deposition may be the initiating event in the cascade of pathologic processes underlying AD, whereas tau pathology appears to be a subsequent event, and more associated with neurodegeneration. Therefore, t-tau and p-tau may be studied as downstream biomarkers of the primary target of anti-amyloid therapies such as gantenerumab.

Although biomarkers indicative of certain neuropathologies are not surrogate markers for efficacy, there is some evidence that anti-$A\beta$ treatments may cause changes in these biomarkers. A neuropathologic study of participants with AD from Study AN1792 suggests that active amyloid immunotherapy ameliorates neurite abnormalities and tau pathology through decreased tau phosphorylation (Serrano-Pozo et al. 2010). In a pooled analysis of CSF data from two Phase II trials with bapineuzumab in participants with mild to moderate AD, a decrease in both p-tau and t-tau levels relative to baseline was observed in the bapineuzumab group after 12 months of therapy (Blennow et al. 2010). These findings were confirmed in two Phase III studies with bapineuzumab (Sperling et al. 2012) as well as in Study WN25203 with gantenerumab. In Study WN23203, CSF biomarkers were analysed for changes in multiple proteins, including $A\beta_{1-42}$, t-tau, p-tau, and neurogranin, over the 2-year period. Markers of neurodegeneration were significantly reduced in the 225-mg gantenerumab group compared with placebo over 2 years, with greater relative reduction in p-tau relative to t-tau. The greatest effect was reduction in p-tau in the 225-mg gantenerumab arm at 2 years relative to the change in the placebo arm. There was no treatment effect on CSF $A\beta_{1-42}$ (Nikolcheva et al. 2015). Because no evidence of efficacy was demonstrated with these therapies in clinical trials yet, changes in these biomarkers provide meaningful information about the pharmacodynamic effects of gantenerumab and the effect on pathologic processes underlying AD.

Based on these data and on the proposed mechanism of action of gantenerumab, levels of CSF t-tau and p-tau and additional exploratory biomarkers reflecting neurodegeneration will be assessed at baseline and following treatment. Because

gantenerumab is expected to clear amyloid from the brain, levels of CSF $A\beta_{1-42}$ will also be measured.

3.3.8.2 Positron Emission Tomography

The definitive diagnosis of AD requires the presence of progressive dementia during life and the postmortem presence of neuropathological lesions (i.e., neuritic plaques composed of β-amyloid aggregates and neurofibrillary tangles formed from hyperphosphorylated tau protein). However, imaging approaches using ligands that demonstrate high affinity for aggregated amyloid are able to provide an assessment of deposition in vivo, which can be evaluated over time (Clark et al. 2011).

3.3.8.3 Brain Volumetry, Connectivity, and Fiber Tract Integrity

A characteristic feature of AD is neuronal destruction. Such neuronal loss is demonstrated at a macroscopic level by progressive cerebral atrophy, which can be tracked on MRI (Fox and Kennedy 2009). Multiple changes in brain anatomy beyond those associated with normal aging have been reported in participants with AD (e.g., enlarged ventricles, decreased cortical thickness, decreased total brain volume, and hippocampal atrophy), and there is evidence for strong correlations between these imaging biomarkers and functional cognitive measures (Li and Wahlund 2011). Based on volumetric MRI measurements, the two most established markers of disease progression in longitudinal observational studies are hippocampal and whole brain atrophy (Fox et al. 2000, 2005; Jack et al. 2010), with ventricular expansion a related quantitative marker.

Therefore, to quantify the effects of gantenerumab on neurodegeneration, whole brain volume, ventricular enlargement, and regional brain volume changes will be assessed at screening and following treatment. All MRI reads and volume measures will be conducted by the central reader.

In addition to the structural brain volume changes, changes in brain functioning of participants will be assessed using a blood oxygenation level-dependent (BOLD) resting-state functional MRI (rs-fMRI) procedure (at sites where this procedure is available) with a paradigm-free procedure (Grecius et al. 2004; Filippi and Agosta 2011). Increased concentrations of Aβ in the brains of participants with AD contribute to neuronal degeneration in the brain over time and have been associated with reduced functional connectivity of various brain networks using rs-fMRI (Sheline et al. 2010; Binnewijzend et al. 2012; Brier et al. 2012; Sheline and Raichle 2013). Resting-state functional connectivity has been found to be decreased in brain regions such as the hippocampus, the default mode network (regions such as precuneus, anterior cingulate, and parietal and temporal cortices), and cortical regions in which the functional connectivity is continuously decreased as disease progresses. It has also been found to be decreased in cognitively normal elderly participants with brain amyloid deposition (PiB+PET scans). Alteration of the decreased brain functional connectivity has been shown using therapeutic interventions such as memantine (Lorenzi et al. 2011) or

donepezil in participants with AD (Goveas et al. 2011; Solé-Padullés et al. 2013). Increased brain functional connectivity was found already after 3 months of treatment with donepezil, which correlated with changes in cognitive measures such as the ADAS-Cog (Goveas et al. 2011; Solé-Padullés et al. 2013). Therefore, therapeutic interventions, which act to remove Aβ from the brains of participants with AD, may help to reverse the altered functional connectivity presumably caused by the accumulation of Aβ in the brain.

The integrity of white matter tracts will be assessed prior to and after treatment with gantenerumab using diffuse tensor imaging (DTI)-MRI techniques. DTI-MRI is based on the measurement of diffusion properties of water molecules in the axonal fiber tracts in white matter. Whereas water molecules can diffuse isotropically in CSF, they are restricted axially in white matter bundles. Widespread group differences in the degree of anisotropic diffusion, or fractional anisotropy (FA), has been seen between participants with AD and healthy subjects (Jack et al. 2015). Greater FA values are thought to indicate greater white matter integrity. Likewise, mean diffusivity, which measures the average rate of diffusion in all directions, has been shown to be higher in AD groups compared with healthy controls, presumably owing to increased white matter injury in participants with AD (Nir et al. 2013).

At sites having the required software and hardware, rs-fMRI (BOLD rs-fMRI) and DTI-MRI will be performed when feasible during the same scanning session as the structural MRI to assess functional brain connectivity and fiber tract integrity before and after treatment with gantenerumab.

4. MATERIALS AND METHODS

4.1 PARTICIPANTS WITH ALZHEIMER'S DISEASE

This study will enroll approximately 1016 participants with increased brain amyloid burden (defined according to CSF or PET criteria), objective memory impairment indicated by cognitive assessment, and a diagnosis of probable AD or prodromal AD based on relevant NIA/AA criteria during the global enrollment phase. Additional criteria are defined in Sections 4.1.1 and 4.1.2.

An increase in sample size may be considered in the event of changes to the sample size assumptions on the basis of blinded data review or factors external to the study.

If at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA during the global enrollment phase, additional participants may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. All participants enrolled at NMPA-recognized sites in the global enrollment phase will be included in the primary analysis. All participants enrolled at NMPA-recognized sites in the global enrollment phase and the China extension phases will be included in a China-specific analysis. Details will be provided in the SAP.

4.1.1 Inclusion Criteria

Participants must meet the following criteria for study entry:

- Ability to provide written consent signed by the participant (co-signed by the participant's legally authorized representative, if required by the local regulations, guidelines, and independent Ethics Committee [EC] or Institutional Review Board [IRB])
- Age 50–90 years old at screening, inclusive
- Availability of a person (referred to as the "study partner" throughout this protocol) who:
  - Agrees to participate throughout the duration of study
  - In the investigator's judgment, has frequent and sufficient contact (e.g., 5 times per week or approximately 10 hours per week) with the participant
  - In the investigator's judgment, is able to provide accurate information regarding the participant's cognitive and functional abilities, including knowledge about domestic activities, hobbies, routines, social skills, and basic activities of daily life; work and educational history; cognitive performance including memory abilities, language abilities, temporal and spatial orientation, judgment and problem solving; emotional and psychological state; and can report any changes in the general health status
  - Agrees to provide information and to complete all aspects of the study at clinic visits (which require partner input for scale completion)
  - Signs the necessary Informed Consent Form(s), and has sufficient cognitive capacity to accurately report on the participant's behavior as well as cognitive and functional abilities
  - Is fluent in the language used at the site and has sufficiently good general health to have a high likelihood of maintaining the same level of interaction with the participant and participation in study procedures throughout the duration of the study

    Every effort should be made to have same study partner participate throughout the duration of the study.
- Fluency in the language of the tests used at the study site
- Willingness and ability to complete all aspects of the study (including MRI, lumbar puncture [if applicable], clinical genotyping, and PET imaging [if applicable])

  The participant should be capable of completing assessments either alone or with the help of the study partner.
- Adequate visual and auditory acuity, in the investigator's judgment, sufficient to perform the neuropsychological testing (eye glasses and hearing aids are permitted)
- Evidence of AD pathological process, as confirmed by CSF tau/$A\beta_{42}$ or on amyloid PET scan by qualitative read by the core/central PET laboratory

- Demonstrated abnormal memory function at screening (FCSRT cueing index $\leq$0.67 and free recall $\leq$27)
- Screening MMSE score $\geq$22 and CDR-GS of 0.5 or 1.0
- Probable AD dementia (consistent with NIA/AA core clinical criteria for probable AD dementia) (McKhann et al. 2011) or prodromal AD (consistent with the NIA/AA diagnostic criteria and guidelines for mild cognitive decline due to AD) (Albert et al. 2011)
- If the participant is receiving symptomatic AD medications, a stable dosing regimen for at least 3 months prior to screening and until randomization

  Participants receiving GV-971 or who are planning to take GV-971 during the study are not eligible
- Agreement not to donate blood or blood products for transfusion for the duration of the study and for 1 year after final dose of study drug
- Agreement not to participate in other research studies for the duration of this trial and its associated substudies
- For enrollment in the China extension, participants must have residence in mainland China, Hong Kong, or Taiwan and be of Chinese ancestry.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<$1% per year during the treatment period and for at least 16 weeks after the last dose of study drug

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $<$1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

4.1.2.1 Exclusions Related to Central Nervous System Disorders

Participants who meet any of the following criteria related to CNS disorders will be excluded from study entry:

- Any evidence of a condition other than AD that may affect cognition, including, but not limited to, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, Parkinson disease, corticobasal syndrome, Creutzfeldt-Jakob disease,

progressive supranuclear palsy, frontotemporal lobar degeneration, Huntington disease, normal pressure hydrocephalus, seizure disorder, delirium or hypoxia

- History or presence of clinically evident systemic vascular disease (e.g., clinically significant carotid/vertebral artery stenosis or plaque, aortic aneurysm), that in the opinion of the investigator has the potential to affect cognitive function
- History or presence of clinically evident cerebrovascular disease (e.g., intracranial or cerebral vascular malformations, aneurysm, intracranial macrohemorrhage)

  Participants with asymptomatic developmental venous anomalies may be eligible after discussion with and approval by the Medical Monitor.
- History or presence of posterior reversible encephalopathy syndrome
- History or presence of any stroke with clinical symptoms within the past 12 months, or documented history within the last 6 months of an acute event that is consistent, in the opinion of the investigator, with a transient ischemic attack
- History of severe, clinically significant (persistent neurologic deficit or structural brain damage) CNS trauma (e.g., cerebral contusion)
- History or presence of intracranial mass (e.g., glioma, meningioma) that could potentially impair cognition
- Presence of infections that affect brain function or history of infections that resulted in neurologic sequelae (e.g., HIV, syphilis, neuroborreliosis, and viral or bacterial meningitis and encephalitis)
- History or presence of systemic autoimmune disorders that potentially cause progressive neurologic disease with associated cognitive deficits (e.g., multiple sclerosis, lupus erythematosus, anti–phospholipid antibody syndrome, and Behçet disease)
- History of schizophrenia, schizoaffective disorder, major depression, or bipolar disorder

  History of major depression is acceptable if participant has had no episode within the past year or is considered in remission or depression is controlled by treatment.
- At risk for suicide in the opinion of the investigator
- Alcohol and/or substance abuse or dependence (according to the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, Version 5) within the past 2 years

  Nicotine use is allowed.

  Marijuana use is not allowed and must be discontinued at least 3 months before screening.

4.1.2.2 Imaging-Related Criteria

Participants who meet any of the following imaging criteria will be excluded from study entry:

- According to the MRI central reader, MRI evidence of any of the following:

  - >2 lacunar infarcts
  - Any territorial infarct >1 cm^3
  - Any white matter lesion that corresponds to an overall Fazekas score of 3 that requires at least one confluent hyperintense lesion on the FLAIR sequence, which is ≥ 20 mm in any dimension
- Combined number of microbleeds and areas of leptomeningeal hemosiderosis (i.e., cumulative ARIA-H) on MRI more than five (and should not include any disseminated leptomeningeal hemosiderosis) based on the review performed by the central reader prior to randomization
- Presence of any other significant cerebral abnormalities, including ARIA-E, as assessed on MRI
- Inability to tolerate MRI procedures or contraindication to MRI, including, but not limited to, presence of pacemakers not compatible with MRI, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan, or any other clinical history or examination finding that, in the judgment of the investigator, would pose a potential hazard in combination with MRI

4.1.2.3 Cardiovascular Disorders

Participants who meet any of the following criteria related to cardiovascular disorders will be excluded from study entry:

- History or presence of clinically symptomatic atrial fibrillation requiring maintenance therapy

  Participants who experienced non-valvular atrial fibrillation that resolved more than 1 year ago and was not associated with prior stroke are eligible.
- Within the last year, unstable or clinically significant cardiovascular disease (e.g., myocardial infarction)

  Heart failure classified as New York Heart Association Class I or II cardiac disease is allowed if not associated with hospitalization within the previous 12 months.
- Uncontrolled hypertension (e.g., blood pressure generally >160 mmHg systolic or >95 mmHg diastolic)

4.1.2.4 Hepatic and Renal Disorders

Participants who meet any of the following criteria related to hepatic and renal disorders will be excluded from study entry:

- Chronic kidney disease, indicated by creatinine clearance <30 mL/min to be calculated by the central laboratory using the Cockcroft-Gault formula at screening, which remains <30 mL/min if retested
- Confirmed and unexplained impaired hepatic function as indicated by screening AST or ALT $\geq 3\times$ the ULN or total bilirubin $\geq 2\times$ ULN

4.1.2.5 Infections and Immune Disorders

Participants who meet any of the following criteria related to infections and immune disorders will be excluded from study entry:

- History of, or known to currently have HIV infection, or hepatitis B or hepatitis C infection that has not been adequately treated in the opinion of the investigator, or history of spirochete infection of the CNS (e.g., syphilis, Lyme disease, or borreliosis)
- Systemically, clinically significantly immunocompromised participants, owing to continuing effects of immune-suppressing medication

4.1.2.6 Metabolic and Endocrine Disorders

Participants who meet any of the following criteria related to metabolic and endocrine disorders will be excluded from study entry:

- Abnormal thyroid function as indicated by abnormal screening tests that are judged to be clinically significant by the investigator, or abnormal thyroid function that requires a new treatment or an adjustment of current treatment

  A participant may be rescreened if there is no improvement in cognition in the investigator's judgment after 3 months of adequate treatment for thyroid function.
- Participants with evidence of folic acid deficiency (as indicated by folic acid level below the lower limit of normal) or vitamin B-12 deficiency (as indicated by vitamin B-12 level below the lower limit of normal and/or methylmalonic acid levels above ULN)

  A participant may be rescreened if there is no improvement in cognition after 3 months of adequate treatment for folic acid or vitamin B-12 deficiency.
- Screening hemoglobin A_{1c} (HbA_{1C}) $>8\%$ (retesting is permitted if slightly elevated) or poorly controlled insulin-dependent diabetes (including hypoglycemic episodes)

  A participant may be rescreened after 3 months to allow optimization of diabetic control.

4.1.2.7 Exclusions Related to Medications

The following medications are prohibited for a pre-specified duration prior to study start, as indicated, and during the entire period of study participation (participants who start these medications during the study may be withdrawn from study treatment):

- Any previous administration of gantenerumab or active immunotherapy (vaccine) that is being evaluated to prevent or postpone cognitive decline
- Any passive immunotherapy (immunoglobulin) or other long–acting biologic agent to prevent or postpone cognitive decline within 1 year of screening
- Any other investigational treatment within 5 half-lives or 4 months prior to screening, whichever is longer
- Any previous administration of GV-971

- Any previous treatment with medications specifically intended to treat Parkinson symptoms or any other neurodegenerative disorder within 1 year of screening and with no plans to initiate such medications prior to randomization

  Certain medications are acceptable if the participant is taking the medicine for a non-neurodegenerative disorder, such as restless leg disorder (e.g., pramipexole).

- Typical antipsychotic or neuroleptic medication within 6 months of screening and with no planned changes prior to randomization except as brief treatment for a non-psychiatric indication (e.g., emesis)

  Atypical antipsychotic medications are not allowed except for intermittent short-term use and will need to be discontinued 2 days or at least 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

- Anticoagulation medications within 3 months of screening with no plans to initiate any prior to randomization

  Anti-platelet treatments (e.g., aspirin, clopidogrel, and dipyridamol) are permitted.

  Short-term, perioperative use of anticoagulant medications will not result in permanent discontinuation from the study; however, *for* any such use *it is recommended to* prospectively *seek advice from* the Medical Monitor and temporary study drug interruption *may be required*.

- Chronic use of opiates or opioids (including long-acting opioid medication) within 3 months of screening with no plans to initiate any prior to randomization

  Intermittent short-term use of short–acting opioid medications for pain is permitted except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

- Stimulant medications (amphetamine, methylphenidate preparations, or modafinil) within 1 month of screening and throughout the study
- Chronic use of benzodiazepines, barbiturates, or hypnotics from 3 months before screening and with no plans to initiate any prior to randomization

  Intermittent short-term use of benzodiazepines, buspirone, or short-acting hypnotic medication for sleep or anxiety is allowed except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

4.1.2.8 Other Exclusions

Participants who meet any of the following criteria will be excluded from study entry:

- Other causes of intellectual disability that may account for cognitive deficits observed at screening (e.g., static encephalopathy, closed brain injury, mental retardation)

  This may be based on, for example, the participant's sufficient education or work experience.

- Pregnancy or breastfeeding, or intention of becoming pregnant during the study

- Deformity of the lumbosacral region of the spine that in the opinion of the investigator would contraindicate lumbar puncture in participants who will have lumbar puncture
- Clinically significant abnormal screening blood, CSF (if applicable), or urine results that remain abnormal at retest
- Impaired coagulation (screening prothrombin time [PT] $> 1.2\times$ the ULN that remains abnormal on retest)
- History of cancer, with the following exceptions:
  - If considered to be cured
  - If not being actively treated with anti-cancer therapy or radiotherapy and, in the opinion of the investigator, is not likely to require treatment in the ensuing 5 years
  - For prostate cancer or basal cell carcinoma, no significant progression over the previous 2 years
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins, including gantenerumab
- Hypersensitivity to any of gantenerumab excipients
- Any other severe or unstable medical condition that, in the opinion of the investigator or Sponsor, could be expected to progress, recur, or change to such an extent that it could put the participant at special risk, bias the assessment of the clinical or mental status of the participant to a significant degree, interfere with the participant's ability to complete the study assessments, or would require the equivalent of institutional or hospital care
- Residence in a skilled nursing facility such as a convalescent home or long-term care facility: Participants who subsequently require residence in such facilities during the study may continue in the study and be followed for efficacy and safety, provided that they have a study partner who meets the minimum requirement

4.1.3 Eligibility for the Open-Label Extension

Participants who have been randomized and who have completed the double-blind treatment period will be eligible to participate in the OLE, provided they do not meet any of the following criteria:

- Discontinued from study treatment during the double-blind treatment period
- Received any other investigational medication during the double-blind treatment period or after the end of double-blind treatment
- Participation in the OLE deemed inappropriate by the investigator (e.g., any serious medical condition or other concerns that preclude the participant's safe participation in the OLE or ability to comply with the required procedures)
- Presence of ARIA-E findings at the Week *116 (or Week 128, if applicable)* MRI scan (participants who have ongoing ARIA-E findings at the Week *116 [or Week 128, if applicable]* will stay in the double-blind treatment period until the finding is deemed

resolved). *For those participants who enroll into the GRADUATE OLE from Week 104, before the double-blind extension took place, eligibility for the OLE would be based on the Week 104 scan.*

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Randomization will be performed centrally using an interactive voice or Web-based response system (IxRS). After screening, participants who meet all eligibility criteria will be randomly assigned to one of two treatment groups (gantenerumab or placebo). The ratio will be 1:1, one active to one placebo. The randomization method will be stratified block-randomization. Randomization to treatment allocation will be stratified by geographic region (Western Europe and Australia vs. Rest of the World vs. North America), participant *APOE* ε4 status (carrier vs. non-carrier), participant stage of disease (prodromal vs. mild AD), use of AD medication (present vs. absent), and participation in the longitudinal amyloid and tau PET substudies. Except in circumstances in which a health authority, EC, or IRB requires it, a participant will not be told of his or her *APOE* ε4 status. Individual participant *APOE* ε4 genotype results will be blinded to participants, investigators, and the Sponsor. *APOE* ε4 status information will be supplied directly to the IxRS vendor by the central testing laboratory so that the information can be incorporated at the time of randomization. For participants for whom *APOE* ε4 status is already known, the results will be blinded to the Sponsor and as much as possible to the site and central MRI reader.

The study is to be conducted in a double-blind manner to minimize potential bias from investigators and participants. The Sponsor will be blinded to study treatment. Sponsor, participants, and site staff will remain blinded to previous treatment allocation in the OLE period. The Master Randomization or Master Medication List will not be available at the study center, to Roche monitors, Roche project statisticians, or to the project team at Roche. Unblinding should not occur except in the case of emergency situations where knowledge of the study drug assigned would affect participant care. The investigator should make every effort to contact Roche before unblinding a participant. In the event that the investigator unblinds a participant without prior notification, the investigator must contact Roche within 1 working day of the event. Any request from the investigator for information about the treatment administered to study participants for another purpose must be discussed with the Medical Monitor.

If unblinding is necessary for participant management (e.g., in the case of a serious adverse event for which participant management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the investigator wants to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event).

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.2.2) that are considered by the investigator or Sponsor to be related to study drug.

4.3 STUDY TREATMENT

The IMP for this study is gantenerumab.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Gantenerumab and Placebo

Gantenerumab and placebo will be supplied by the Sponsor as liquid formulation ready for SC administration. Packaging of the study drug will be overseen by the Roche Clinical Trial Supplies Department and will bear a label with the identification required by local law, the protocol number, study drug identification, and dose. The packaging and labeling will be in accordance with Roche standard and local regulations. Upon receipt of the investigational products at the site, site personnel should check the product for damage and verify the proper identity, quantity, and integrity of the study drug. Site personnel should report any deviations or product complaints to the monitor upon discovery. For further details, please refer to the Gantenerumab Investigator's Brochure.

For information on the formulation and handling of gantenerumab, see the pharmacy manual and Gantenerumab Investigator's Brochure.

4.3.2 Dosage, Administration, and Compliance

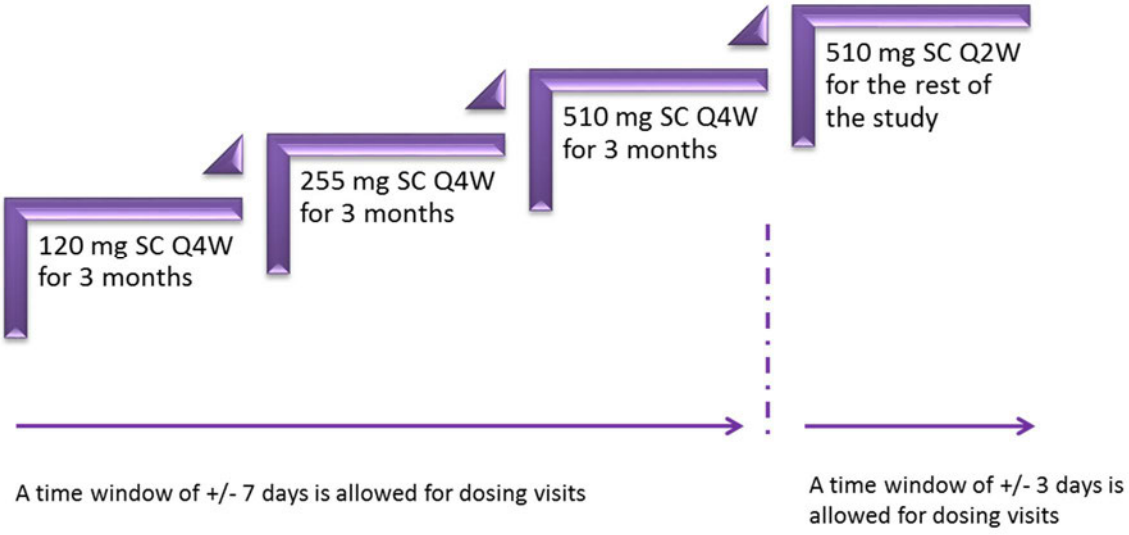
4.3.2.1 Gantenerumab and Placebo Administration during Double-Blind Treatment Period

Gantenerumab or placebo will be administered by SC injection to all participants.

Gantenerumab will be administered by SC injection to all participants randomized to the active treatment arm, regardless of *APOE* ε4 status, at a dose of 120 mg SC Q4W for 3 months, 255 mg SC Q4W for 3 months, and 510 mg SC Q4W for 3 months, prior to reaching the target dose (see Figure 8). Once the target dose is reached, study drug will be administered every 2 weeks (Q2W administration of 510 mg SC gantenerumab). The switch to a Q2W administration schedule allows decreasing the number of SC administrations in the abdomen per visit.

Note: A minimum of 3 doses during each dosing step must be administered prior to uptitration.

Figure 8 Overall Gantenerumab Dosing Design in the Double-Blind Treatment Period



Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous.

For Q4W injections, a time window of ±7 days is allowed for dosing visits. For Q4W injections, the recommended minimum time between doses is 3 weeks. The maximum recommended time between doses should not exceed 6 weeks. Once study drug is administered Q2W, the time window for dosing visits is ±3 days. For Q2W injections, the recommendation is not to administer more than 1020 mg (i.e., 2 times 510 mg Q2W) within 28 days. Always return to the initial planned schedule per randomization for subsequent visits.

Regardless of dose, each participant will undergo up to a total of 49 dosing visits in scenario 1 or 55 dosing visits in scenario 2 (if applicable, see Section 3.3.1) in the double-blind treatment period of the study. Participants who have completed the double-blind treatment period at the time of the implementation of *the 12 week study extension*, will have undergone up to 43 dosing visits. Injections will be administered as one 0.8-mL (120-mg dose), one 1.7-mL (255-mg dose), or two 1.7-mL injections (510-mg dose) subcutaneously to the abdomen, respectively.

Placebo of identical composition (except protein) and identical volume to gantenerumab will be administered by SC injection to all participants randomized to placebo at the same frequency and using the same route of administration.

On study drug administration days that include efficacy assessments (see the schedule of activities in Appendix 1), study drug must be administered at the clinical site. Study

personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

At applicable sites, study drug may be administered by a trained nursing professional at the participant's home or another suitable location, if the participant has given written informed consent to participate in home nursing visits.

Rules for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.2.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.2.2 Gantenerumab and Placebo Administration during the Open-Label Extension Period

During the OLE, participants previously randomized to the active treatment arm will continue to be administered the study drug every two weeks (Q2W administration of 510 mg SC gantenerumab). Participants previously randomized to the placebo arm will be required to undergo 9 months of uptitration.

In order to maintain the previous study treatment blinding (Sponsor, site, and participant), all participants will be dosed every two weeks in the OLE as illustrated in Table 4. As in the double-blind treatment period, a safety MRI has to be performed before each uptitration to ensure that the participant can be uptitrated safely to the next dose.

To ensure blinding to previous treatment, gantenerumab and/or placebo will be administered every 2 weeks as one 0.8-mL and two 1.7-mL injections or two 1.7-mL injections subcutaneously to the abdomen. Injections may contain active gantenerumab or placebo to ensure the correct total dose of active gantenerumab at each visit (see Table 4).

Note: As in the double-blind part, a minimum of 3 doses during each dosing step must be administered prior to uptitration. During uptitration in the OLE, a minimum of 3 doses of each dosing step also have to be administered prior to be eligible for uptitration**. In the OLE, a dose is defined as two consecutive dosing visits (one with an even dose number and one with an odd dose number, see Table 4).**

Table 4 Overall Gantenerumab Dosing Design in the Open-Label Extension

		Open-Label Extension																	
	Visit	Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Wk 26	Wk 28	Wk 30	Wk 32	Wk 34
	Dose Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Participants previously on placebo	Dose	120 mg Q4W						255 mg Q4W						510 mg Q4W					
	Injections (mL)	1× 0.8A + 2× 1.7P	1× 0.8P + 2× 1.7P	1× 0.8A + 2× 1.7P	1× 0.8P + 2× 1.7P	1× 0.8A + 2× 1.7P	1× 0.8P + 2× 1.7P	1× 1.7A + 1× 1.7P	2 × 1.7P	1× 1.7A + 1× 1.7P	2× 1.7P	1× 1.7A + 1× 1.7P	2× 1.7P	2× 1.7A	2× 1.7P	2× 1.7A	2× 1.7P	2× 1.7A	2× 1.7P
Participants previously on active	Dose	510 mg Q2W																	
	Injections (mL)	2× 1.7A + 1× 0.8P	2x 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A

A = Active treatment; Num = number; P = placebo; Wk = week

For the OLE, the time window for dosing visits is ± 3 days. Always return to the initial planned schedule per randomization for subsequent visits.

Rules for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.2.

Participants enrolled in the WN39658 OLE study will have to complete the full titration scheme (i.e., at least 12 weeks on each dosing step) prior to being able to enroll in the WN42171 open-label study where they will receive 510 mg SC Q2W.

On study drug administration days that include efficacy assessments (see the schedule of activities in Appendix 1), study drug must be administered at the clinical site. Study personnel who prepare and administer the study drug must not be involved with any efficacy assessments or safety evaluations.

At applicable sites, study drug may be administered by a trained nursing professional at the participant's home or another suitable location if the participant has given written informed consent to participate in home nursing visits.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

PET Tracers

All participants who are enrolled in PET substudies will be assessed by PET imaging using an appropriate PET ligand. For screening, the possible amyloid PET ligands will be florbetapir, florbetaben, and flutemetamol. According to E.U. guidance, the PET tracers, as used in the context of this study, are designated as non-IMP. In some regions, according to local regulations, these PET tracers may be considered to be IMP.

In countries where the PET radioligands are approved for marketing, the approved local product information will be provided, and in countries where they are not approved for marketing, the Investigator's Brochures will be provided.

For the safety reporting requirements dealing with the PET tracers used in this study, please refer to Section 5.7).

Details about the PET substudies are described in separate protocols.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (gantenerumab or placebo) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to Gantenerumab

The Sponsor will offer continued access to Sponsor study drug (gantenerumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A participant will be eligible to receive Sponsor study drug (gantenerumab) after completing the study if all of the following conditions are met:

- The participant has a life-threatening or severe medical condition and requires continued Sponsor study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the participant
- The participant and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A participant will not be eligible to receive Sponsor study drug (gantenerumab) after completing the study if any of the following conditions are met:

- The Sponsor study drug is commercially marketed in the participant's country and is reasonably accessible to the participant (e.g., is covered by the participant's insurance or wouldn't otherwise create a financial hardship for the participant)
- The Sponsor has discontinued development of the drug or data suggest that the drug is not effective for AD
- The Sponsor has reasonable safety concerns regarding the drug as treatment for AD
- Provision of the drug is not permitted under the laws and regulations of the participant's country
- Participant is eligible to enroll in an ongoing gantenerumab open-label study

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

All eligible participants will be offered to receive gantenerumab as part of an extension study, as described in Section 3.1.

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a participant from 3 months prior to screening to the study completion or discontinuation visit. All such medications (including name, dose, administration schedule, start and end dates) should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Participants are eligible for study participation whether or not they are receiving approved medication for AD (i.e., acetylcholinesterase inhibitors, memantine, and/or medical food supplements, where approved) with the exception of GV-971. Participants who are receiving GV-971 or who are planning to receive GV-971 during the study are not eligible. Information about background AD medication (e.g., drug name, dose, and start and stop dates, reason for interruption or modification) has to be captured on eCRF. Randomization will be stratified for participants taking and not taking approved anti-dementia medications.

Adding a new medication or changing the dose of a medication after randomization should occur only for the treatment of an adverse event or in case of AD progression. Whenever possible, a medication listed below should be used if appropriate.

The following medications are permitted if the dose and dose regimen have been stable for at least 3 months prior to screening and are expected to remain stable after screening or if required for treatment of an adverse event after randomization:

- Anticonvulsant medications for an approved pain indication
- Selective serotonin reuptake inhibitors for the treatment of depressive symptoms
- Over-the-counter and/or herbal medications, food additive, or any other agent or supplement intended to improve cognition or reduce cognitive decline
- Medications used to treat a mood or anxiety disorder given as maintenance treatment (with the exception of benzodiazepine)
- Intermittent use of short-acting (non-extended release) opioid medications for pain except within 2 days or 5 half-lives (whichever is the longer) of any cognitive assessment (up to a maximum of 3 consecutive days per month)
- Intermittent use of benzodiazepines, including alprazolam, lorazepam, oxazepam, triazolam, or temazepam, or a one-time dose of diazepam or a short–acting hypnotic medication (e.g., zolpidem) if use is intermittent for sleep or anxiety, except within 2 days or 5 half-lives (whichever is the longer) prior to any cognitive assessment
- A dose of benzodiazepine for pre-surgical and pre-imaging sedation at appropriate visits if allowed by the EC or IRB

- Intermittent use of centrally acting antihistamine medications except within 2 days or 5 half-lives (whichever is the longer) prior to any cognitive assessment
- Under certain circumstances, initiation of anti-hemostasis medications during the study conduct

  Anticoagulation therapy lasting no longer than 3 weeks (e.g., temporary usage during surgery) is permitted. Nevertheless, anticoagulation therapy *may require temporary study drug interruption and advice from the Medical Monitor is recommended*.

Concomitant and excluded therapies for determination of participant eligibility are described in Section 4.1.2.7.

Participants who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

4.4.2 Prohibited Therapy

Any medication that is prohibited before screening is also prohibited during conduct of the study (see Section 4.1.2.7). If a participant receives any prohibited treatment during the study, the participant may be withdrawn from study treatment.

4.5 STUDY ASSESSMENTS

Refer to Appendix 1 for the schedule of activities to be performed during the study.

At applicable sites, certain study assessments may be performed by a home nursing (HN) professional at the participant's home or nursing center to improve access and convenience for participants participating in the study. The Sponsor has selected a healthcare company that is responsible for providing HN services for participating sites (the HN vendor). The HN vendor is responsible for ensuring that all HN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that HN services are appropriate for a participant and the participant gives written informed consent to participate in HN visits, the HN network communicates with the participant and the participant's site. HN visits are scheduled on specified visit days to allow relevant assessments to be performed by the HN professional. The schedule of activities (see Appendix 1) specifies which assessments may be performed by an HN professional.

4.5.1 Informed Consent Forms and Screening Log

All participants and study partners must review, sign, and date the most current IRB/EC-approved written informed consent for participation in the study before any study-specific prescreening assessments, screening tests or evaluation are performed. Informed Consent Forms for enrolled participants and their study partners and for those who are not subsequently enrolled will be maintained at the study site.

All prescreening and screening evaluations must be completed and reviewed to confirm that participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants prescreened and screened and to confirm eligibility or record reasons for screening failure, as applicable. Prescreening is optional and is covered by a dedicated Informed Consent Form.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), smoking history, use of alcohol, and drugs of abuse. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant within 3 months prior to screening visit will be recorded. Demographic data will include age, sex, and self-reported race/ethnicity. Medical history and demographic data will be collected at the screening visit only.

As this study is being conducted in multiple geographic regions, it is likely that participants of different ethnic origins will be enrolled in the study. Although there is currently no indication that gantenerumab is metabolized or eliminated differently or that the treatment effect would be different in participants of different ethnic origins, collecting this information is essential to adequately evaluate the results of this study (e.g., possible differences in PK exposure [concentration of the drug in the blood] or treatment effect).

4.5.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary (optional), and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

The schedule of activities indicates when complete physical examinations (including neurological systems) are to be recorded (see Appendix 1).

Limited, symptom-directed physical examinations should be performed per the schedule of activities (or as clinically indicated). Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

In addition, weight will be obtained at screening, and at every visit at which creatinine clearance is tested as well as at any other visit as deemed necessary by the investigator. Height will be obtained at screening only.

4.5.4 Vital Signs

Vital signs will include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements.

Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

Vital sign measurements may be performed by an HN professional.

The schedule of activities indicates when vital signs (blood pressure and pulse rate) are to be recorded (see Appendix 1).

4.5.5 Cognitive, Functional, and Health Economics Assessments

The assessments described in this section will be performed as outlined in the schedule of activities (see Appendix 1) and in the order specified in Section 4.6.

Whenever possible, there should be consistency in the rater and study partner who complete the scales for each participant throughout the duration of the study. Potential raters will receive training and be approved by the rating scale contract research organization (CRO) prior to being allowed to administer any cognitive assessments or rating scales in the study.

Whenever possible, cognitive and functional assessments should be performed at the visit timepoints indicated in the schedule of activities (see Appendix 1). However, in exceptional circumstances for post-randomization visits, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per the schedule of activities, they may be performed up to 4 weeks out of window.

Given that the primary outcome measure in this trial involves subjective judgment, the adequacy of participant and study partner interviews and ratings will be monitored by an endpoint reliability program administered by the rating scale vendor; this is considered an essential part of good research methodology. For the primary endpoint as well as for some other scales, audio recordings may be used for quality assurance purposes. Prior studies have clearly demonstrated that the failure to adequately monitor such ratings can substantially increase the risks of failed trials (Becker and Greig 2008; Kobak 2010).

4.5.5.1 Clinical Dementia Rating Scale

The CDR global score (CDR-GS) characterizes a participant's level of impairment according to the following categories: 0 (normal), 0.5 (very mild dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia). The SOB score is a detailed quantitative general index that provides more information than the CDR-GS in

participants with mild dementia (Berg 1988; Morris et al. 2001, O'Bryant et al. 2010) and is scored from 0–18 with higher scores indicating greater impairment. The CDR characterizes six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The necessary information to make each rating is obtained through a semi-structured interview with the participant and a reliable informant or collateral source (e.g., a study partner).

As much as is feasible, the CDR should be administered to an individual participant by the same assessor throughout the study and that assessor should not perform the MMSE, ADAS-Cog, Verbal Fluency Task, Coding, FAQ, or Alzheimer's Disease Cooperative Study Group–Activities of Daily Living (ADCS-ADL). However, if in exceptional circumstances only this assessor is available to perform these other scales, then the CDR participant interview must be completed after the study partner interview but before ADAS-Cog, MMSE, Verbal Fluency Task, Coding, and other scales are completed. Nevertheless, at screening, baseline, Week 104, Week 116 or Week 128 (if applicable), the CDR rater cannot perform other scales than the CDR. In addition, the CDR rater should not be involved in safety assessments and especially should not receive information about any ARIA findings.

4.5.5.2 Alzheimer's Disease Assessment Scale–Cognitive Subscale

The ADAS-Cog is the most frequently used scale to assess cognition in clinical trials for mild to moderate AD dementia (Rozzini et al. 2007; Connor and Sabbagh 2008; Ihl et al. 2012). More specifically, the ADAS-Cog is a participant-based assessment that measures learning and memory, language production, language comprehension, constructional praxis, ideational praxis, and orientation. The modified version will be used; it has 13 items and includes the addition of delayed word recall and a number of cancellation subtests, as well as use of only one trial for word recognition (Mohs et al. 1997). Equivalent alternate forms of the word recall, word recognition, and number cancellation subtests will be used in successive test administrations.

4.5.5.3 Mini-Mental State Examination

The MMSE is a set of standardized questions used to evaluate possible cognitive impairment and help stage the severity level of this impairment (Folstein et al. 1975). The questions target six areas: orientation, registration, attention, short-term recall, language, and constructional praxis/visuospatial abilities. The MMSE is a participant-based assessment.

4.5.5.4 Free and Cued Selective Reminding Test–Immediate Recall

The FCSRT-Immediate Recall (FCSRT-IR) is a participant-based assessment that measures memory under conditions that control attention and cognitive processing. Impairments in FCSRT-IR performance have been associated with preclinical and early dementia in several longitudinal epidemiological studies (Grober and Buschke 1987; Sarazin et al. 2007). The 16-word version of the test will be used in this study.

4.5.5.5 Verbal Fluency Task

The category verbal fluency (e.g., animals) is a participant-based assessment that measures speed and flexibility of verbal thought. Verbal fluency tests are sensitive tools for detecting dementia (Pasquier et al. 1995; Lezak et al. 2004) and for monitoring decline over time (Clark et al. 2009).

4.5.5.6 Coding

The Coding, also called Digit Symbol Substitution Test (or DSST), is a subtest from the Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV; Wechsler 2008). The Coding is a participant-based assessment that measures speed of processing and associative memory. The test is known to be sensitive to disease progression (Lezak et al. 2004). The 120-second version of the test will be used in this study.

4.5.5.7 Functional Activities Questionnaire

The FAQ (Pfeffer et al. 1982) is an informant-based measure of functional abilities. Informants provide performance ratings of the target person on ten complex higher-order activities.

4.5.5.8 Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory

The ADCS-ADL (Galasko et al. 1997) is the scale most widely used to assess functional outcome in participants with AD (Vellas et al. 2008). The ADCS-ADL is a 23-item informant-based questionnaire that covers both basic ADL (e.g., eating and toileting) and more complex ADL or instrumental ADL (e.g., using the telephone, managing finances, preparing a meal). It has a 4-week recall period. Total scores range from 0–78, with higher scores indicating better functioning.

4.5.5.9 Zarit Caregiver Interview–Alzheimer's Disease

The Zarit Caregiver Interview–Alzheimer's Disease (ZCI-AD) is a modified version of the Zarit Burden Interview, which was originally designed to reflect the stresses experienced by caregivers for people with dementia (Zarit and Zarit 1990). The modified version includes slight modifications in item and title wording (e.g., removal of "your relative" to refer directly to the participant, removal of "burden" from title) and the use of 11-point numerical rating scales. The ZCI-AD scale consists of 30 items and is completed by the study partner without involvement from the site staff. It has a 4-week recall period.

4.5.5.10 Quality of Life–Alzheimer's Disease

The Quality of Life–Alzheimer's Disease (QoL-AD) was developed to assess QoL in participants who have dementia (Logsdon et al. 1999, 2002). The QoL-AD consists of 13 items covering aspects of participants' relationships with friends and family, physical condition, mood, concerns about finances, and overall assessment of QoL. The total score is the sum of the 13 items and ranges from 13–52, with higher scores indicating better HRQOL.

In this study, the QoL-AD will be administered in a standardized, structured interview format to participants by investigative staff in order to gather participant responses about QoL. The study partner will also complete the study partner version of the questionnaire to enable proxy responses from the study partner.

4.5.5.11 EQ-5D

The EuroQoL–Five Dimensions (EQ-5D) is a standardized measure of health status designed to provide a simple generic measure of health for clinical and economic appraisal. It is broadly applicable across a wide range of health conditions and treatment.

The EQ-5D assesses five domains to provide a health state index. These are anxiety/depression, pain/discomfort, usual activities, mobility, and self-care.

The following two versions will be used in this study:

- EQ-5D-5L Proxy, Version 1: The study partner (the proxy) is asked to rate the participant's health-related QoL in his or her (the proxy's) opinion.
- EQ-5D-5L, Self-Complete Version: The study partner is asked to rate his or her own health-related QoL.

4.5.5.12 Resource Utilization in Dementia Scale

The Resource Utilization in Dementia (RUD) scale (Wimo et al. 2003) aims to document formal and informal resource use in a clinical trial setting. The RUD-Lite captures the most important elements in dementia care: accommodation, informal care, hospitalizations, and community care services. Information on study partner sociodemographics in addition to working status and effect on productivity will be collected. The amount of informal care will be collected according to three types of care: personal ADL, instrumental ADL, and supervision. Data on accommodation and temporary changes in accommodation during the last month and the duration of these will be collected according to four levels of accommodation: own home, intermediate forms of accommodation, dementia-specific residential accommodation, and nursing home. Resource utilization will be recorded as the number of nights spent in different types of hospital wards, the number of visits to the most common types of outpatient care, and the number of visits in community care services.

4.5.5.13 Neuropsychiatric Inventory Questionnaire

The Neuropsychiatric Inventory–Questionnaire (NPI-Q) (Kaufer et al. 2000) was developed to assess a wide range of behaviors encountered in dementia participants, to provide a means of distinguishing severity of behavioral changes, and to facilitate rapid behavioral assessment through the use of screening questions. It is an informant-based instrument in which 12 behavioral domains are evaluated. The recall period is the past month, and severity scores range from 0–36, with higher scores indicating greater severity. The study partner's distress portion of the scale will not be used in this study.

4.5.5.14 Electronic Assessment of Rating Scales

The following rating scales will be captured electronically and transferred to the database directly from the core laboratory: ADAS-Cog, Verbal Fluency Task, ADCS-ADL, CDR, MMSE, FCSRT, FAQ, AD QoL, EQ-5D, RUD-Lite, NPI-Q, and CSSR-S.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

4.5.6.1 Standard Laboratory Samples

Samples for the following laboratory tests will be sent to a central laboratory for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

- Serum chemistry: AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory)

  HbA_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed according to the schedule of activities.
- Hematology: hemoglobin, hematocrit, RBC count (with morphology), WBC count, platelets, basophils, eosinophils, lymphocytes, monocytes, neutrophils, and WBC–other total counts
- Screening serology: HIV, hepatitis B, and hepatitis C
- Coagulation: PT
- Urine for drugs of abuse: At screening only, urine samples will be analysed for the presence of the following drugs: amphetamine, benzodiazepines, cannabinoids, opiates, cocaine, barbiturates, and methadone. Results will be used to verify participant eligibility pertaining to drugs of abuse. Inconclusive results may be repeated once during the screening period. Investigators should use their best clinical judgment in cases where results may be erroneous (e.g., permitted use of opiates or ingestion of food/food supplements).
- Urinalysis: At screening only, urinalysis will be performed at the site by dipstick for blood, protein, glucose, and pH. Microscopic examination will be performed by the central laboratory if blood and/or protein results are positive or strongly positive.
- Urine for pregnancy test: Urine pregnancy testing will be performed at each dosing visit (prior to dose administration) for women of childbearing potential (including those who have had a tubal ligation), and at the site for any other female participants if required by local regulations. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory.

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

4.5.6.2 Biomarker Sampling

Samples will be obtained from all participants and will be used for research purposes to identify dynamic biomarkers that may be predictive of response to treatment with gantenerumab (in terms of dose, safety, and tolerability) and will help to better understand the pathogenesis, course, and outcome of AD and related diseases.

For participants who consent to the optional Roche Research Biosample Repository (RBR) residual biomarker samples will be kept for future biomarker research (see Section 4.5.12).

The procedures for the collection, handling, and shipping of biomarker samples are specified in the Sample Handling and Logistic Manual.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.12), biomarker samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Roche may keep information about screening test results, medical history, and demographic information for all participants (including non-eligible participants) for future development of diagnostic tests related to Aβ, *APOE* genotype, and AD, as well as additional analyses.

Cerebrospinal Fluid and Serum Sampling (for CSF-Enrolled Participants Only)

CSF samples and matching serum samples will be obtained from participants who choose to provide CSF samples during screening (CSF-enrolled participants) for confirmation of Aβ and tau levels for eligibility purposes (mandatory) and for monitoring Aβ and tau levels, as well as other CSF biomarkers at different timepoints during the study. The matching serum samples may be used to determine parameters that allow the assessment of the blood-brain barrier status and/or inflammatory processes in the brain, such as CSF/serum albumin ratio, CSF/serum IgG and IgM indices, and oligoclonal bands. CSF and serum samples will be collected according to the schedule of activities (see Appendix 1). Lumbar puncture will be performed by an individual who meets all local requirements and is proficient in the procedure. Lumbar puncture procedures and post–lumbar puncture care will be performed in accordance with local practice. CSF sampling should be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters. Procedures for the processing of the CSF samples can be found in the Sample Handling and Logistics Manual.

Approximately 12 mL of CSF will be collected at each timepoint. The sample will be divided into aliquots onsite and used for the following:

- Central measurement of gantenerumab levels in the CSF and biomarker analysis, including $A\beta_{1-42}$, t-tau, p-tau, as well as some exploratory markers. Samples may also be used to support the development of biomarker assays for diagnostic use.

Unused CSF samples will be kept for future biomarker research if the participant gives consent to participate in the RBR (see Section 4.5.12.5).

Clinical Genotyping

During screening, three mandatory 3-mL whole blood samples will be obtained for DNA extraction from every participant who has consented to participate in the study. All participants will be evaluated for *APOE* ε4 status, clusterin (apolipoprotein J) genotypes, and Fcγ-receptor genotype. The Fcγ-receptor genotype may play a role in PK and PD variability of antibody-based therapeutic agents and may be predictive of response and non-response.

APOE ε4 status will be determined and will be blinded to the Sponsor, investigator, and participant and will not be shared with the investigator or the participant until the study is unblinded (unless required for participant safety or by the relevant health authority or IRB/EC). Participants will have access to this information if they elect to at the end of the study. If already known, the *APOE* ε4 status will still need to be confirmed and should be kept blinded from the Sponsor. In addition, as much as possible, participant *APOE* ε4 status should remain blinded to the site and central MRI readers.

Samples and data may be used for future research or diagnostic test development.

RNA Sampling

During screening and at a subsequent visit as detailed in the schedule of activities (see Appendix 1), two 2.5-mL whole blood samples will be obtained for RNA extraction from every participant who has consented to participate in the study. The sample may be used to evaluate clusterin messenger RNA and other exploratory genetic markers in peripheral blood (see Section 4.5.12).

Plasma Sampling

At screening and at subsequent visits as detailed in the schedule of activities (see Appendix 1), two 6-mL whole blood sample will be obtained for plasma extraction from every participant who has consented to participate in the study.

This sample will be used to evaluate exploratory plasma biomarkers in peripheral blood, which may include, but will not be limited to Aβ, tau, $p\text{-}Tau,\ and$ neurofilament.

An additional plasma sample for the assessment of exploratory plasma biomarkers will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes

aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

4.5.6.3 Anti-Drug Antibody Sampling

Blood samples will be collected to assess the possible development of ADAs in all participants as noted in the schedule of activities (see Appendix 1). Plasma samples will be analysed for antibodies to gantenerumab using a bridging ELISA.

Samples collected from participants receiving placebo will not be assessed in the first instance but retained for subsequent analysis if appropriate.

Unused sample material may also be used for the purposes of current ADA assay improvement.

The procedures for the collection, handling, and shipping of ADA samples are specified in the Sample Handling and Logistics Manual supplied to the site.

4.5.6.4 Pharmacokinetic Sampling

Plasma Gantenerumab Samples

Blood samples will be collected to evaluate the pharmacokinetics of gantenerumab in plasma as noted in the schedule of activities (see Appendix 1).

An additional PK sample for the assessment of plasma concentrations of gantenerumab will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E, or occurrence of ARIA-H meeting discontinuation criteria.

Samples from participants receiving placebo may not be assessed at once but will be retained for subsequent analysis if appropriate. Samples will not be analysed in real time but will be batched for analysis throughout the study.

Unused sample material may be used for the purpose of current gantenerumab assay improvement, for the quantification of specific gantenerumab glycan species, and for the assessment of exploratory plasma biomarkers.

The procedures for the collection, handling, and shipping of PK samples are specified in the Sample Handling and Logistics Manual supplied to the site.

Cerebral Spinal Fluid for Assessment of Gantenerumab Concentration (for Participants Enrolled on the Basis of CSF Criteria Only)

For participants enrolled on the basis of CSF criteria and willing to perform lumbar puncture in the schedule of activities, an aliquot of CSF obtained by lumbar puncture, described in Section 4.5.6.2, will be allocated for the measurement of gantenerumab concentration. Samples from participants receiving placebo may not be assessed at once but will be retained for subsequent analysis if appropriate.

Unused sample material may also be used for the purposes of current assay improvement.

4.5.7 Electrocardiograms

Single 12-lead ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the participant has been resting in a supine position for at least 5 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws, brain MRI scans, and lumbar puncture). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site.

The centrally provided electrocardiograph machine should record the following: heart rate, QRS duration, and RR, PR, and QT intervals and transferred to the Sponsor database from the core laboratory.

4.5.8 Columbia–Suicide Severity Rating Scale

The C-SSRS (http://www.cssrs.columbia.edu) is an assessment tool used to assess the lifetime suicidality of a participant (C-SSRS at baseline) as well as any new instances of suicidality (C-SSRS since last visit). The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual or potential lethality. The C-SSRS baseline will be collected at baseline and the C-SSRS since the last visit will be collected at subsequent visits as indicated in the schedule of activities (see Appendix 1).

The assessment will be completed by a certified C-SSRS rater after he or she interviews the participant and the participant’s study partner during the study visit.

4.5.9 Brain Magnetic Resonance Imaging

MRI should be performed using 1.5-T or 3.0-T scanners, and wherever possible the same scanner should be used for an individual participant for the full duration of the study. MRI will be conducted at participant screening for safety monitoring, as a baseline measure of structural brain volumes, and as baseline information for the PET substudies (for the schedule of activities, see Appendix 1).

Where available, exploratory MRI techniques including rs-fMRI and DTI will also be acquired. In addition, the screening MRI will be used to help determine whether the exclusion criteria are met (e.g., number of microbleeds, presence of mass lesions).

MRI will be used during the study to help assess safety such as the occurrence of microbleeds or signs potentially indicative of inflammation or ARIA-E. Additional unscheduled MRI scans may be performed to better understand relevant CNS adverse events (such as increased confusion) occurring in the context of ARIA or to follow a sign that emerges at a scheduled scan; contrast agent may be used in such a case of follow-up MRI scans if administration of contrast agent is considered safe for the participant according to local standards. In addition, structural MRI (to assess whole brain and regional brain atrophy), fMRI, and DTI-MRI will be performed at multiple timepoints to determine potential treatment effects on MRI outcome measures (according to the schedule of activities).

MRI scans will include the following sequences:

- 3D T_1-weighted gradient recalled echo (GRE) scans
- T_2*-weighted GRE scans
- T_2-weighted FLAIR scans
- BOLD rs-fMRI, if available (to assess resting-state functional connectivity at investigative sites having the required software and sequences)
- DTI-MRI, if available (to assess fiber tract integrity)

For details on the specific imaging sequences and acquisition times required, refer to the MRI Manual.

MRI should not be performed unless at least 3 days have passed since a lumbar puncture. If an MRI and lumbar puncture are both scheduled for the same day, the MRI should be performed first.

All images (except BOLD fMRI and DTI-MRI) will be used to assess MRI inclusion and exclusion criteria.

MRI scans will be reviewed by a central MRI core laboratory, which will perform the diagnostic reads and assessment of MRI outcome measures. MRI scans should preferably be transferred to the central MRI core laboratory electronically. Data transfer from individual study sites to the central MRI core laboratory may take up to 7−10 days, if not done electronically. Upon receipt of the MRI scans from the study sites, the central MRI core laboratory will provide the diagnostic reads. MRI results must be made available to investigators prior to next dosing (refer to Section 5.1.2 for additional details on MRI safety management).

MRI facility qualification and scan quality control will be performed by the central MRI core laboratory.

Additional instructions regarding the procedures for MRI scan acquisition and transmittal to the central reading facility can be found in the MRI Manual.

4.5.10 Healthy Volunteer Magnetic Resonance Imaging Scans for Site Qualification

As part of site qualification, one to two volunteers (preferably two) at each site should be recruited and scanned using the same machine and the same sequences to be used for site qualification before any participant is scanned in this study. The choice of healthy volunteers is at the discretion of the investigator and/or the imaging center, and the volunteer must provide written consent to take part in the scanning calibration. Volunteers must not have any contraindications for MRI scanning (evaluation per local procedures at the imaging site), and they will not be enrolled in the study or undergo any other assessments as part of the trial. If volunteer scans are acquired, then they will be reviewed for suitable image quality and used for qualitative comparison with additional scans with the same volunteer acquired after certain events as follows: at the time of a major upgrade to the site's scanner, any other event deemed significant enough to affect image quality, or per central reader guidance. This procedure will help ensure consistency in scanning quality over the duration of the study. Two volunteers are ideal in case one volunteer is no longer readily available for test scanning.

Additional instructions regarding the procedures for MRI facility qualification can be found in the MRI Manual.

4.5.11 Positron Emission Tomography Scan

A PET scan will be performed for confirmation of Aβ levels for eligibility purposes in participants (PET-enrolled participants). Three radioligands are be used for screening purposes: [^{18}F] florbetapir (Amyvid™), [^{18}F] flutemetamol (Vizamyl™), and [^{18}F] florbetaben (Neuraceq™).

Screening PET scans must not be acquired prior, potentially exclusionary screening results are available in order to minimize radiation burden to participants. In order to allow sufficient flexibility for scheduling of the screening PET scan screening procedures (including central reading of the MRI scans) ideally should be completed within 2–3 weeks before the screening PET scan is required.

A positive PET scan using [^{18}F] florbetapir, [^{18}F] flutemetamol, or [^{18}F] florbetaben acquired outside this study protocol may be permissible to confirm participant inclusion with Medical Monitor approval. Previously acquired PET scans must meet quality standards detailed in the PET Technical Operations Manual and must be centrally evaluated.

Detailed instructions regarding the procedures for PET scan methodology, including scanning procedures can be found in the PET Technical Operations Manual.

4.5.12 Optional Samples for Research Biosample Repository

4.5.12.1 Overview of the Research Biosample Repository

The RBR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for participants in the future.

Specimens for the RBR will be retained from participants who give specific consent to participate in this optional research.

RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.12) will not be applicable at that site.

4.5.12.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to gantenerumab or AD:

- Leftover blood from Clinical Genotyping sample and clinical RNA sample and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), plasma biomarker sample, CSF samples, and serum samples

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing, or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analysed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.12.4 Confidentiality

Specimens and associated data will be labeled with a unique participant identification number.

Participant medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR specimens, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.12.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature

will be required to document a participant's agreement to provide optional RBR specimens. Participants who decline to participate will not provide a separate signature.

The investigator should document whether or not the participant has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.12.6 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. If a participant wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the participant's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The participant will be provided with instructions on how to withdraw consent after the trial is closed. A participant's withdrawal from Study WN39658 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a participant's withdrawal from the RBR does not constitute withdrawal from Study WN39658.

4.5.12.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to participant participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TIMING OF STUDY ASSESSMENTS

4.6.1 Screening and Pretreatment Assessments

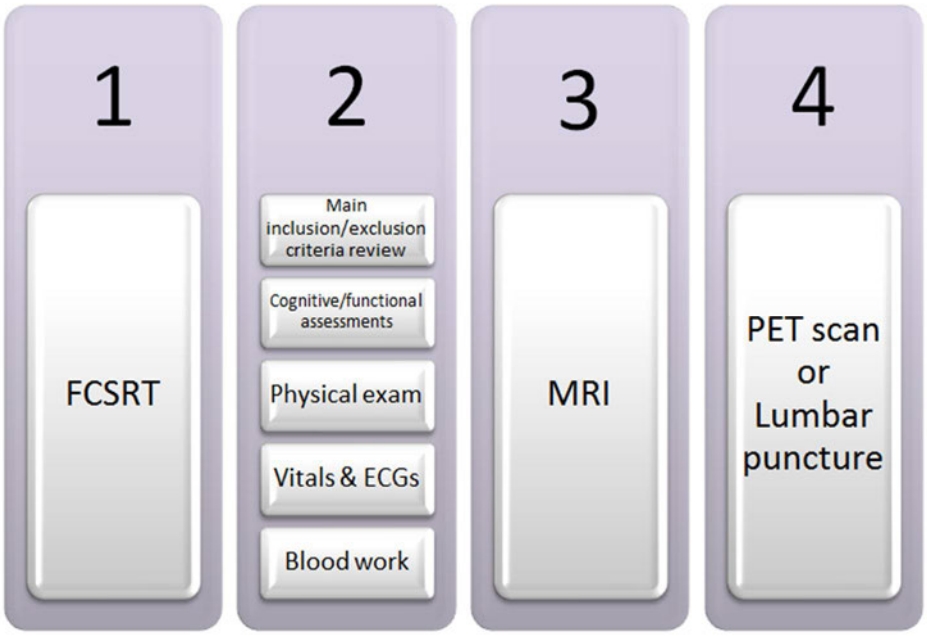
Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled participants and for participants who are not subsequently enrolled will be maintained at the study site. After providing written informed consent, participants who are willing to participate in the study will undergo all screening assessments within 12 weeks prior to the baseline visit, as detailed in the schedule of activities (see Appendix 1). Participants must fulfill all the entry criteria for participation in the study and the results must be available prior to the baseline visit.

The FCSRT and MMSE assessments may also be completed at prescreening. However, in this case, a separate prescreening consent would need to be signed and FCSRT and MMSE would not need to be repeated during the screening process. In case the participant would not qualify based on the FCSRT inclusion criteria, investigators have the option to repeat the FCSRT once after at least 6 months have elapsed if recruitment for the study is still ongoing. Rescreening of participants who failed MMSE is not allowed.

In case of an abnormal laboratory or ECG result at screening that may normalize upon retest, investigators have the option to repeat the tests (prior to baseline and within the 12-week screening window) once to confirm the test results before randomizing a participant at baseline.

In rare cases in which an MRI scan needs to be repeated or any other unexpected delay due to logistical or technical reasons, the screening period may be extended by some days. Extending the screening period beyond 12 weeks must be approved by the Medical Monitor and should be for exceptional circumstances only; careful scheduling should remain a priority.

The recommended order of screening assessments is as follows:



ECG = electrocardiogram; FCSRT = Free and Cued Selective Reminding Test; MRI = magnetic resonance imaging; PET = positron emission tomography.

The recommended order of clinical assessments and rating scales at screening is shown below.

Participant Assessments	Study Partner Assessments
1. FCSRT (performed at prescreening or at screening) 10-min break (optional) 2. MMSE (performed at prescreening or at screening) 3. CDR (participant interview)	CDR (study partner input)

CDR = Clinical Dementia Rating; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination.

CSF sampling, PET scan, and MRI scan at screening should be performed only once all other screening results are available and none exclude the participant from the trial.

If a participant does not qualify on the basis of applicable tests, the participant may be rescreened again after at least 3 months (6 months for FCSRT) have elapsed if recruitment for the study is still ongoing.

As noted in the exclusion criteria (see Section 4.1.2), participants may be rescreened after appropriate treatment if they were originally excluded for abnormal thyroid, folic acid, vitamin B-12, or HbA_{1c} results. Other laboratory tests that would exclude the participant may be repeated once (as an unscheduled laboratory assessment) if it is suspected that the abnormal result is transient and likely to be normal on repeat.

Participants may be rescreened if the protocol is amended such that they would satisfy the amended criteria and if recruitment for the study is still ongoing. In this case, all screening assessments must be repeated with the exception of lumbar puncture (if performed within the previous 12 months for this study and within eligible ranges) and PET scan within eligible ranges. Given that *APOE* status will not change over time, there is no need to repeat clinical genotyping in case of rescreening.

Participants may be rescreened if there is a substantial change in the participant's condition (e.g., a disallowed medication was stopped) and if recruitment for the study is still ongoing and all eligibility criteria are met.

It is suggested that screening tests with the exception of the lumbar puncture, MRI scan, and PET scan be performed within 1 to 2 weeks of signing the Informed Consent Form (to allow adequate time for the remaining tests). As soon as all the results are available, and none exclude the participant from the trial, CSF collection and/or PET scan and MRI scan should be performed, if required.

It will take several days to receive the results of the MRI or CSF. On occasion, the originally scheduled MRI or CSF collection day may need to be postponed and in the case of the MRI, it may need to be repeated. Therefore, the scheduling of these tests needs to be done carefully and should begin as soon as possible.

For participants enrolling on the basis of PET criteria, and for participants willing to participate in any of the PET substudies, scans can be obtained after all other screening results are available. For these participants, it is recommended that the MRI appointment should be scheduled to allow sufficient time for the PET scan to be performed and evaluated before the end of the screening period.

A positive PET scan using Amyvid™, Vizamyl™, or Neuraceq™ acquired outside this study may be permissible to confirm participant inclusion with Sponsor approval. Previously acquired PET scans must meet quality standards detailed in the PET Technical Operations Manual and must be centrally evaluated.

Roche may keep information about screening test results, medical history, and demographic information for all participants (including non-eligible participants) for future development of diagnostic tests related to Aβ, *APOE* genotype, and AD, as well as additional analyses.

4.6.2 Assessments at Baseline

In order to be randomized and to receive double-blind treatment, participants must have no significant change in medical, psychiatric, or neurological conditions or change in medication since screening. The recommended order of assessments and rating scales is as follows:

- Clinical assessments (e.g., CDR, MMSE, and ADAS-Cog), including all those that require study partner input, should be completed before any invasive safety assessments.
- Vital sign measurements, ECGs, blood draws for clinical laboratory assessments, PK, ADA, and plasma biomarker sampling, and urine samples are recommended to be conducted following scale assessments and *all* must be performed prior to study drug administration.

The recommended order of clinical assessments/rating scales at baseline is as follows:

Participant Assessments	Study Partner Assessments
1. ADAS-Cog13	1. CDR (study partner input)
2. CDR (participant interview)	2. FAQ
10-min break (optional)	3. ADCS-ADL
3. MMSE	4. ZCI-AD
4. Coding	5. QoL-AD
5. Verbal Fluency Task	6. EQ-5D
10-min break (optional)	7. RUD-Lite
6. QoL-AD	8. NPI-Q
7. C-SSRS	

ADAS-Cog13 = Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living; CDR = Clinical Dementia Rating; C-SSRS = Columbia–Suicide Severity Rating Scale; EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; NPI-Q = Neuropsychiatric Inventory–Questionnaire; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

If assessments are split over 2 days, all safety assessments must be performed on the same day as the study drug administration.

4.6.3 Assessments during the Double-Blind Treatment Period

In the double-blind treatment period, participants will receive up to 49 (in scenario 1) or 55 (in scenario 2, if applicable) SC administrations of study drug over the course of 114 or 126 (if applicable) weeks, respectively. The final on-treatment efficacy and safety assessments are scheduled 2 weeks after the last dose. Participants who have completed the double-blind treatment period at the time of the implementation of *the study extension by 12 weeks* received up to 43 doses and underwent the final efficacy and safety assessments at Week 104, 2 weeks after the last dose.

The same recommended order of clinical assessments and rating scales as above for the baseline visit should be followed (omitting those that are not conducted per the schedule of activities; see Appendix 1). *However, in exceptional circumstances, for post-randomization visits, if the caregiver, the primary rater or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.*

Vital sign measurements, ECGs, blood draws for clinical laboratory assessments, PK, ADA, plasma biomarkers, and urine must be performed prior to study drug administration. *They are also recommended to be conducted following scale assessments.*

If assessments are split over 2 days, all safety assessments must be done on same day as the treatment administration.

On each dosing day, after all assessments prior to dosing have been completed (see the schedule of activities in Appendix 1), gantenerumab or matching placebo will be administered subcutaneously at room temperature. For the first four doses, participants should be observed for a minimum of 2 hours after dosing and then for a minimum of 1 hour after all remaining doses (i.e., Doses 5 and beyond). Participants should leave the study center after injections only if they appear to be tolerating the injections. When doses are to be administered remotely from the clinical sites, study drug administration may be performed only by qualified health care providers, as defined by local regulations, who must remain with the participants for a minimum of 1 hour after each injection and be equipped with rescue medications.

Rescue medications to treat anaphylactic and anaphylactoid reactions must be available at the site or at the dosing location for HN visits. Participants and their study partners will be alerted to watch for signs of anaphylactic and anaphylactoid reactions and to contact the study center as soon as possible if any such signs are noted.

Visits at which the participant receives study drug may take place within ±7 days of the protocol-specified date for Q4W administration and ±3 days of the protocol-specified date for Q2W administration per the schedule of activities in Appendix 1. For Q4W injections, the recommended minimum time between doses is 3 weeks. The maximum recommended time between doses should not exceed 6 weeks. For Q2W injections, the recommendation is not to administer more than 1020 mg (i.e., 2 times 510 mg Q2W) within 28 days. Always return to initial planned schedule per randomization for subsequent visits.

All visits should be scheduled as close as possible to the exact day. It is preferred that all assessments for a visit be performed on the same day, but if necessary, assessments may be performed over more than 1 day. Preferably, all clinical scales and assessments should be performed on the same day. Study drug administration should be performed only after all assessments and rating scales for the participant have been completed.

For sites and participants for whom this is practical, visits that require only dosing, vital sign measurements, urine pregnancy test, C-SSRS assessment, and adverse event assessment may be performed at an alternate location conducted by appropriate health care professionals.

Refer to Appendix 1 for the schedule of activities during the treatment period.

4.6.4 Assessments during Open-Label Extension Period

The same recommended order of clinical assessments and rating scales as in the double-blind treatment period (see Appendix 1), as well as vital sign measurements,

ECGs, blood draws for clinical laboratory assessments, PK, ADA, plasma biomarkers, and urine samples must be performed prior to study drug administration. *They are also recommended to be conducted following scale assessments.* If assessments are split over 2 days, all safety assessments must be performed on the same day as the treatment administration.

On each dosing day, after all assessments prior to dosing have been completed (see Appendix 1), gantenerumab and/or matching placebo will be administered subcutaneously at room temperature. For the first eight doses, participants should be observed for a minimum of 2 hours after dosing and then for a minimum of 1 hour after all remaining doses (i.e., doses 9 and beyond). Participants should leave the study center after injections only if they appear to be tolerating the injections. When doses are to be administered remotely from the clinical sites, study drug administration may be performed only by qualified health care providers, as defined by local regulations, who must remain with the participants for a minimum of 1 hour after each injection and be equipped with rescue medications.

Rescue medications to treat anaphylactic and anaphylactoid reactions must be available at the site or at the dosing location for HN visits. Participants and their study partners will be alerted to watch for signs of anaphylactic and anaphylactoid reactions and to contact the study center as soon as possible if any such signs are noted.

In the OLE, visits at which the participant receives study drug may take place ±3 days of the protocol-specified date for Q2W administration per the schedule of activities in Appendix 1. Always return to the initial planned schedule per randomization for subsequent visits.

For sites and participants for whom this is practical, visits that require only dosing, vital sign measurements, urine pregnancy test, C-SSRS assessment, and adverse event assessment may be performed at an alternate location conducted by appropriate health care professionals.

Refer to Appendix 1, Table 3 for the schedule of activities during the OLE.

4.6.5 Procedures for New MRI Findings

In addition to any local reading according to local procedures and requirements, all MRI scans will be reviewed by an expert central reader within approximately 1 week of receipt and a report provided to the site. For the purposes of overall study relevant decisions and recommendations, including participant eligibility as well as for analysis, results from the expert central reader will be used. Any time the central reader identifies a new MRI finding the study center medical staff and the Sponsor will be rapidly notified (see Section 4.5.9).

Refer to Section 5.1.2 for instructions in the event of new MRI findings (ARIA-E and ARIA-H).

4.6.6 Assessments at Study Completion or Early Termination Visit

Participants who complete the double-blind treatment period at Week 114 in scenario 1 or at Week 126 in scenario 2 (if applicable) will have to complete the final efficacy and safety assessment period 2 weeks following the last dose. Some participants may have already received the last study drug administration at Week 102 and performed the final efficacy and safety visit at Week 104 at the time of implementation of *the study extension by 12 weeks*.

All participants will be asked to come back for the follow-up assessments 14 weeks and 50 weeks after the last dose, unless they are transitioning to an OLE.

All participants who withdraw from treatment or discontinue from the study early (during the double-blind treatment period or during the OLE) will be asked to return 2 weeks after the last dose of study drug in order to complete the early termination visit.

In addition, participants who withdraw from treatment will be asked to return for collection of safety (except MRI) and limited efficacy data (i.e., the primary and secondary endpoints) at visits that have efficacy assessments per the schedule of activities until the end of the double-blind treatment period or until the last OLE follow-up visit (OLE Follow up 2) for those who enrolled in the OLE period.

Autopsy reports, including cause of death, for all participants who die during the study (i.e., prior to the Week 50 follow-up visit) should be requested.

Refer to the schedule of activities to be performed at the study completion in Appendix 1.

4.6.7 Follow-Up Assessments

Participants who complete the double-blind treatment period and who are not willing to enroll in an OLE or these who complete the OLE period (defined as administration of at least three 510-mg doses Q4W) and are not willing to enroll in the WN42171 open-label study will be asked to return to the clinic 14 weeks and 50 weeks after the last dose of study drug for the follow-up visits (Follow Up 1 and Follow Up 2 or OLE Follow Up 1 and OLE Follow Up 2, respectively)..

When participants complete the treatment period or discontinue early, every effort should be made to ensure that the safety follow-up period and all related assessments are completed.

After the study completion or early termination visit, adverse events should be followed as outlined in Sections 5.5 and 5.7. Refer to the schedule of activities (see Appendix 1) for the list of assessments to be performed at the follow-up visits.

4.6.8 Unscheduled Assessments

Assessments at unscheduled visits should be determined by the investigator based on clinical relevance and appropriateness to the cause of the unscheduled visit. The schedule of activities in Appendix 1 allows for all assessments to be performed at unscheduled visits.

4.7 TREATMENT, PARTICIPANT, STUDY, AND SITE DISCONTINUATION

4.7.1 Study Treatment Discontinuation

Participants must discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the participant
- Pregnancy
- Upon evidence of more than 15 ARIA-H, cumulatively
- Any disseminated leptomeningeal hemosiderosis

All participants who withdraw from treatment will be asked to return 2 weeks after last dose in order to complete the early termination visit assessments.

In addition, participants who withdraw from treatment will be asked to return for collection of safety (except MRI) and limited efficacy data (i.e., the primary and secondary endpoints) at visits that have efficacy assessments according to the schedule of activities until the end of the double-blind treatment period*, and then the follow-up visits,* or until the last OLE follow-up visit (OLE Follow Up 2) for those who enrolled in the OLE.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue study treatment prematurely will not be replaced.

4.7.2 Participant Discontinuation

Participants have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a participant from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Participant withdrawal of consent at any time
- Study termination or site closure
- Any medical condition that the investigator *and* Sponsor determines may jeopardize the participant's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the participant

- Participant non-compliance with the study and/or study procedures, defined as missing more than three consecutive dose administrations (with Q4W dosing regimen) or more than six consecutive dose administrations (with Q2W dosing regimen) because of non–safety-related reasons or more than half of the dosing visits in a calendar year

All participants who discontinue from the study early will be asked to return 2 weeks after last dose in order to complete the early termination visit.

Participant should be informed of circumstances under which their participation may be terminated by the investigator without the participant's consent. Any administrative or other reasons for withdrawal must be explained to the participant.

Every effort should be made to obtain information on participants who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, participants will not be followed for any reason after consent has been withdrawn.

Participants who withdraw from the study will not be replaced.

4.7.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to participants
- Participant enrollment is unsatisfactory
- Futility analyses suggesting that treatment with gantenerumab is likely not effective.
- Sponsor determines it is the best interest of the participants.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.7.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all participants have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Gantenerumab is not yet approved, and clinical development is ongoing. The safety plan for participants in this study is based on clinical experience with gantenerumab in completed and ongoing studies. The identified risks for gantenerumab are outlined below. Please refer to the Gantenerumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of participants enrolled in this study. Eligibility criteria have been designed to exclude participants at higher risk for imaging-related abnormalities. Participants will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Gantenerumab

5.1.1.1 Amyloid-Related Imaging Abnormalities

To date, clinical experience with gantenerumab reveals that ARIA events are dose-dependent and *APOE* ε4 dependent. These events are manageable with MRI monitoring and dose intervention algorithms. In addition, in case of clinical symptoms, the use of IV glucorticosteroids may be considered.

Rules for management of participants who develop ARIA-E or ARIA-H are provided in Appendix 6.

5.1.1.2 Injection-Site Reactions

Gantenerumab may cause a reaction when given as an SC injection. In studies with gantenerumab, the most common events occurring more frequently with gantenerumab than with placebo were local ISRs, such as injection-site erythema. The majority of events were of mild intensity and resolved without treatment (see Section 1.2.3 for details).

Detailed information on the characteristic signs and symptoms of ISRs (e.g., erythema, pruritus) will be recorded on the dedicated eCRF page (see Section 5.3.5.2 for details on recording of ISRs).

5.1.1.3 Immunogenicity

As with administration of any exogenous protein, there is the potential for the development of ADAs, which can be neutralizing and/or sensitizing and which can potentially lead to febrile or allergic reactions, including anaphylaxis. The immunogenic risk of gantenerumab is considered low since it is a fully human antibody.

There are no clinical findings indicative of an immunogenic response to gantenerumab. Participants should be told how to recognize the signs and symptoms of hypersensitivity reactions and be monitored.

5.1.2 Management of Participants Who Experience Selected Adverse Events

Participants will undergo brain MRI examinations prior to every dose increase (pre-uptitration MRI scans) and according to the schedule of activities once the target dose is achieved. The pre-uptitration MRI scans will determine eligibility for the next uptitration dose. In the double-blind treatment period, a minimum of 3 doses of each dosing step have to be administered before the participant is eligible for the next uptitration dose. In the OLE, a minimum of 3 doses of each dosing step must be administered prior to be eligible for uptitration. In the OLE, a dose is defined as two consecutive dosing visits (one with an even dose number and one with an odd dose number, see Table 4, Section 4.3.2.2).

Participants will be eligible for uptitration if there are no new ARIA-E, if the ARIA-E is resolved (BGTS=0), and if the criteria for discontinuation because of ARIA-H have not been met.

In addition, the following dose adjustment and discontinuation rules for MRI findings will apply:

- In case of asymptomatic ARIA-E ≥1 and <4 BGTS: Continue study drug at the same dose level (i.e., do not uptitrate) and repeat MRI 4 weeks later.

  As long as BGTS is <4 and ≥1, continue study drug at the same dose level and continue MRI monitoring at 4-week intervals until the event resolves. When ARIA-E resolves, resume uptitration and MRI monitoring according to the schedule of activities.

  If BGTS ≥4 or symptoms develop, refer to the rule below.

- In case of occurrence of symptoms in the presence of ARIA-E (any size) or asymptomatic ARIA-E with ≥4 BGTS: Temporarily interrupt study drug (but continue all assessments per schedule of activities) and implement MRI monitoring performed at 4-week intervals until symptoms and ARIA resolve.

  When symptoms and ARIA-E resolve, reintroduce study drug at the next scheduled dosing visit, at the same dose given at the time the event was detected and perform an MRI scan after the first dose for participants on Q4W regimen and after the second dose for participants on the Q2W regimen.

  If no new ARIA-E is detected, resume uptitration and obtain an MRI scan per the titration schedule. For participants on the Q2W regimen, perform another MRI scan 3 months after study drug reintroduction.

- In exceptional cases of 1) an ARIA-E that is asymptomatic with BGTS <4 and that is considered stable over consecutive MRI images by the Sponsor and investigator; or 2) symptomatic ARIA-E for which the imaging evidence of ARIA-E has resolved but

the CNS symptoms continue, the study drug can either be reintroduced or uptitrated, as applicable, and 4-weekly MRI monitoring may no longer be necessary, as determined by the Sponsor and investigator.

- Symptomatic ARIA-E is defined as onset or worsening of CNS symptom(s) that is/are temporally associated with ARIA-E MRI findings.
- Any recurrence of ARIA-E: Treat using the same procedures as for the first event (based on symptoms and BGTS).
- Participants who develop >15 ARIA-H cumulatively will be discontinued from study drug (the cumulative number should not include any disseminated leptomeningeal hemosiderosis, i.e., up to 3 focal leptomeningeal hemosiderosis *either on the same scan or cumulatively*; a focal leptomeningeal hemosiderosis is counted as an ARIA-H).
- In cases where both ARIA-E and ARIA-H occur, the most conservative approach should be followed.
- A PK sample and a plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or ARIA-H that meet the discontinuation criteria.
- The investigators may choose to perform additional MRI monitoring for ARIA at any time.
- MRI monitoring of ARIA findings should be conducted at approximately 4-week intervals.
- Any other new significant findings will be reviewed by the medical monitor and appropriate dose action will be taken.

The iDMC reviews the incidence of ARIA in an unblinded manner and may recommend adjustment of dosing regimen and/or ARIA management for the overall study population or for a specific *APOE* ε4 genotype.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a

pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the participant at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.12)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the participant's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe; the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.8)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.2.4 Selected Adverse Events

Data on associated symptoms and safety MRI scans will be collected for the following selected adverse events:

- ARIA-E: ARIAs suggestive of vasogenic edema and sulcal effusions
- ARIA-H: ARIAs suggestive of microhemorrhages and/or hemosiderin deposits

Please refer also to Section 5.3.5.1 for further details how to report ARIA events.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4). The investigator is also responsible for reporting medical device complaints (see Section 5.4.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each participant contact. All adverse events, whether reported by the participant, the study partner, or noted by study

personnel, will be recorded in the participant's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

In addition, after administration of a PET ligand, but prior to initiation of study drug, the following adverse events should be reported:

- All adverse events (serious or non-serious) believed to be related to a PET ligand
- All serious adverse events occurring within 48 hours of PET ligand administration regardless of relatedness to the PET ligand

For reporting of serious adverse events, see Section 5.4.2 for instructions. For non-serious PET ligand adverse events, a PET ligand specific non-serious adverse event reporting paper form should be completed and submitted to the Sponsor or its designee by scanning and emailing the form using the email address provided on the form.

After initiation of study drug, all adverse events will be reported until the participant's last visit (including long-term follow-up visits).

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all participant evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

Table 5 provides guidance for assessing adverse event severity.

Table 5 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating “yes” or “no” accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 ARIA Findings

Not every ARIA finding qualifies as an adverse event. An ARIA finding must be reported as an adverse event if it meets any of the following criteria:

- Symptomatic ARIA-E (i.e., accompanied by CNS symptoms), and/or
- ARIA findings that result in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation), and/or

- Findings that are otherwise clinically significant in the investigator's judgment

Any accompanying symptoms should also be captured as separate adverse events.

It is the investigator's responsibility to review all ARIA findings.

Observations of the same clinically significant ARIA finding should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.2 Injection Reactions

Injection reactions (local and systemic) are defined as adverse events that occur during or within 24 hours after study drug administration that are judged to be related to the study drug injection.

For local reactions, the diagnosis of injection site reaction should be captured on the Adverse Event eCRF, and associated signs and symptoms (e.g., erythema at injection site) should be recorded on the dedicated Injection Site Reaction eCRF.

Systemic reactions should be recorded as a single diagnosis on the Adverse Event eCRF (e.g., anaphylactic reaction). If possible, avoid ambiguous terms such as "systemic reaction."

5.3.5.3 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.4 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.5 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.6 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5× ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., “elevated potassium,” as opposed to “abnormal potassium”). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.7 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator’s judgment

It is the investigator’s responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.8 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy’s Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.9 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of AD.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed to progression of AD, "Alzheimer's disease progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.10 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.11 Lack of Efficacy or Worsening of Alzheimer's Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is because of disease progression, it should be reported as an adverse event.

5.3.5.12 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization due to expected progression of underlying disease
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The participant has not experienced an adverse event

5.3.5.13 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a study drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.14 Clinical Outcome Assessment Data

Adverse event reports will not be derived from clinical outcome assessment (COA) data by the Sponsor, and safety analyses will not be performed using COA data. Sites are not expected to review the COA data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Medical device complaints (see Section 5.4.4 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor: [redacted], *MBBS, PhD* (Primary)

Mobile Telephone No.: [redacted]

Medical Monitor: [redacted]*., MSc* (Secondary)

Mobile Telephone No.: [redacted]

To ensure the safety of study participants, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours

per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.

In addition, the following serious adverse events should be reported after administration of a PET ligand and prior to initiation of study drug:

- All serious adverse events believed to be related to the PET ligand
- All serious adverse events occurring within 48 hours of the PET ligand administration, regardless of relatedness to the PET ligand.

The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until the participant's last visit (including long-term follow-up visits). Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Participants

Female participants of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 16 weeks after the last dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female participant exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 Reporting Requirements for Medical Device Complaints

The investigator must report all medical device complaints (e.g., devices for study drug administration) to the Sponsor. The investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward

the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the pharmacy manual for further details). If the medical device results in an adverse event to the study participant, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

5.5 FOLLOW-UP OF PARTICIPANTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the participant is lost to follow-up, or the participant withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as the participant's last study visit), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously

communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the reference safety information in the documents listed below:

Drug	Document
Gantenerumab	Gantenerumab Investigator's Brochure
[^{18}F] Florbetaben (Neuraceq™)	[^{18}F] Florbetaben Investigator's Brochure
[^{18}F] Flutemetamol (Vizamyl™)	[^{18}F] Flutemetamol Investigator's Brochure
[^{18}F] Florbetapir (Amyvid™)	[^{18}F] Florbetapir Investigator's Brochure
[^{18}F] GTP1	[^{18}F] GTP1 Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The purpose of this study is to investigate the treatment effect of gantenerumab relative to placebo. The primary efficacy analysis will be based on an intent-to-treat (ITT) population, which will include all randomized participants during the global enrollment phase, with participants grouped according to their randomly assigned treatment.

Approximately 1016 participants will be randomized in the global enrollment phase of this study. An increase in sample size may be considered in case of changes to sample size assumptions based on blinded data review or factors external to the study.

If at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA during the global enrollment phase, additional participants may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in the China.

The primary analyses of this study will include participants enrolled during the global enrollment phase; data from participants enrolled during the China extension will not be included in the primary analyses.

Details of the planned statistical analyses mentioned below will be fully specified in a separate SAP, which will be finalized prior to the locking and unblinding of the study database.

6.1 DETERMINATION OF SAMPLE SIZE

Determination of sample size is based on participants enrolled in the global enrollment phase. In this study, approximately 1016 participants will be enrolled and randomized in 1:1 ratio to each treatment arm (gantenerumab or placebo) during the global enrollment phase. A sample size increase may be considered if factors external to the study or blinded study data review would warrant a change to the sample size assumptions.

Additional participants may be randomized during the China extension if at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA during the global enrollment phase.

The estimated sample size required to demonstrate efficacy with regard to CDR-SOB is based on the following assumptions:

- The mean change in the CDR-SOB from baseline to Week 104 is 2.5 points in the placebo arm
- A common standard deviation across treatment arms for change of approximately 2.97 from baseline to Week 104 in the CDR-SOB
- Gantenerumab has a true effect of a 30% relative reduction in deterioration of CDR-SOB

Based on these assumptions, and using a student's T-test with equal variance, a sample size was calculated for 90% power to detect a true treatment effect of 30% relative reduction in deterioration of CDR-SOB at a two-sided α of 0.05.

Uncertainties on parameters affecting the power (e.g., dropout rate, study drug discontinuation rate, standard deviation, and placebo decline) were assumed to be equivalent to a drop-in sample size of up to around 35% and were corrected for accordingly. This calculation leads to a total of 1016 participants in the study.

At the date of writing Protocol Version 4, it is expected that participants *would have missed* an average of 8 weeks of study drug administration over the course of the original 2-year study due to the COVID-19 pandemic. This has the potential to decrease the power of the study from ~90% to ~80%. To mitigate the impact of missed administrations, the double-blind treatment period *was* extended by 12 weeks. Under current assumptions, this brings the study power back to the originally planned ~90%.

The sample size may be increased from 1016 up to 1322 participants (661 participants per arm). The decision whether to increase sample size will be based on blinded study data review, e.g., by a review of the frequency of missed study drug administrations due to the COVID-19 pandemic. Further details will be described in the SAP. The

assessment will be performed by the Sponsor at a specified timepoint. The sponsor will remain blinded. The sample size will not be reduced on the basis of this assessment. Other factors external to the study may also trigger a decision to increase sample size.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, participant disposition, and incidence of protocol deviations will be summarized for the ITT population according to the randomly assigned treatment arms.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (such as age, sex, race, disease stage, *APOE* ε4 status, use, and non-use of background therapy for AD) will be summarized descriptively for the ITT population, grouped according to the assigned treatment arm.

Descriptive summaries of continuous data will present the mean, standard deviation, median, and minimum and maximum. Descriptive summaries of discrete data will include frequencies expressed in terms of number and percentage of participants.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will use the ITT population, with participants grouped according to the treatment assigned at randomization.

6.4.1 Primary Efficacy Endpoint

The primary efficacy outcome measure is the change in CDR-SOB from baseline (Day 1) to Week 116. In the case where the double-blind treatment period is extended for an additional 12 weeks, the primary efficacy outcome measure will be the change in CDR-SOB from baseline (Day 1) to Week 128.

The clinical question of interest is to assess the study treatment effect on disease progression up to Week 116 (or Week 128, if applicable), irrespective of use or initiation of symptomatic treatments for AD, in the absence of the COVID-19 pandemic.

In accordance with the estimand framework outlined in the ICH-E9 addendum (EMA 2018), the attributes of the estimand for the primary endpoint are defined as follows:

- *Population: early (prodromal to mild) AD population including all randomized participants.*
- *Variable: change from baseline at Week 116 (or Week 128) in the CDR-SOB*
    - *Treatment: prescribed study drug including uptitration to the target dose, irrespective of use or initiation of symptomatic treatment for AD.*
- *Intercurrent events (ICE): the list of ICE will be defined in the SAP, this includes:*
    - *Treatment discontinued for study drug or condition–related (SDCR) reasons (e.g., treatment-related adverse event or lack of efficacy):*

- *Treatment discontinued for non-SDCR (NSDCR) reasons (e.g. purely administrative reason)*

- *Population level summary: mean change from baseline to Week 116 (or Week 128, as appropriate) between gantenerumab-treated participants and placebo-treated participants.*

The primary estimand is a combination of a treatment-policy strategy and a hypothetical strategy (FDA 2017) to account for the different assumptions for each type of ICE, SDCR or NSDCR.

Full details of the primary estimand, and of the corresponding estimator and estimation methods (e.g. statistical model, multiple imputation for missing or excluded data points) will be provided in the SAP. Supplementary estimands may also be considered and will be defined in the SAP.

Every effort will be made to minimize missing data. Furthermore, the Sponsor *has made* every effort to expedite the implementation of *the 12 week extension to the* double-blind treatment period. If the study is extended by an additional 12 weeks (for a total extension of 24 weeks), the number of patients in scenario 1 (who will have missing Week 128 efficacy data) will be minimized.

Participants who discontinue early from study treatment will be asked to return for collection of safety and limited efficacy data (i.e., the primary and secondary efficacy endpoints) until the end of the double-blind treatment period and follow-up visits.

Descriptive summaries of the number of participants with missing data, the number of participants in each scenario, the timing, and reasons for discontinuation from the study will also be provided by treatment group.

Additional details will be documented in the SAP.

6.4.2 Secondary Efficacy Endpoints

The absolute change from baseline in the continuous secondary efficacy endpoints listed in Section 2, Table 2 (including cognition/function endpoints, global endpoints, disease pathology biomarkers, and endpoints measuring other AD symptoms and effects) will be analysed using an *approach* similar to that described above for the primary efficacy endpoint.

In order to protect the overall type I error rate for the study when incorporating the hypothesis testing of the primary endpoint and secondary endpoints into the analysis, the fixed sequence testing procedure (Westfall and Krishen 2001) will be used to adjust for multiple comparisons. The first endpoint that will be tested is:

- Change from baseline to Week 116 in CDR-SOB

In the case where the double-blind treatment period is extended for an additional 12 weeks, the primary efficacy outcome measure will be the change in CDR-SOB from baseline (Day 1) to Week 128.

The order of testing for other secondary endpoints will be defined in the SAP.

The treatment difference in the primary endpoint (the change from baseline to Week 116 in the CDR-SOB) will be tested at a two-sided 5% overall significance level. If this test result is statistically significant, the secondary endpoints will be tested for significance in the predefined order as specified in the SAP. If any test result is not statistically significant, testing of the subsequent endpoints will not occur.

6.4.3 Exploratory Efficacy Analyses

Subgroup analysis of efficacy results will be performed for subgroups defined by age, sex, race, stage of disease (prodromal AD vs. mild AD), *APOE* ε4 status, geographic region, use and non-use of background therapies for AD, and other clinically relevant factors at baseline.

The efficacy endpoints collected during the Study WN39658 open-label treatment phase and during Study WN42171 *may* be combined with data from the Study WN39658 double-blind treatment phase in order to evaluate change from baseline beyond the end of the double-blind treatment period and to evaluate the effect of a delayed start of treatment with gantenerumab.

6.4.4 Pharmacodynamic and Exploratory Biomarker Analyses

PD and exploratory biomarker endpoints will be analysed using descriptive statistics, subgroup analysis, or statistical models if appropriate. For longitudinally measured endpoints, the change from baseline and the difference between participants randomized to gantenerumab and participants randomized to placebo will be estimated if appropriate.

Prior to the completion of the study, a separate PD cutoff date may be established to allow expedient sample analyses and early access by third party vendors.

Exploratory biomarkers may be reported separately.

6.5 SAFETY ANALYSES

The safety-analysis population will include all randomized participants who receive at least one dose of study drug, with participants grouped according to the treatment actually received, as defined in the SAP.

- Incidence, nature, and severity of MRI safety findings: ARIA-E and ARIA-H
- Incidence, nature, severity, and timing of injection-site reactions
- Incidence, nature, and severity of serious adverse events
- Incidence, nature, and severity of adverse events

- Incidence of adverse events of special interest
- Incidence of treatment discontinuations due to adverse events
- Mean changes in clinical laboratory tests from baseline over time; incidence of treatment-emergent abnormal laboratory values and abnormal laboratory values reported as adverse events
- Mean change in ECG assessments from baseline over time and incidence of abnormal ECG assessments
- Physical and neurologic examination abnormalities
- Mean change in vital signs (blood pressure, pulse rate) from baseline over time and incidence of abnormal vital sign measurements
- Changes in CSSR-S scores from baseline over time
- Number and proportion of participants with ADAs during the study relative to the number and proportion of participants with ADAs at baseline

Prior to completion of the study a separate ADA cutoff date may be established to allow expedient samples analyses and early access by third party vendors. The ADA cutoff date will be applied when there is sufficient ADA sample data available to adequately assess immunogenicity.

6.6 PHARMACOKINETIC ANALYSES

Plasma concentration data for gantenerumab *may* be tabulated and summarized. Descriptive summary statistics will include the arithmetic mean, median, range, SD, and coefficient of variation, as appropriate. Because a sparse PK sampling design is being used, population (non-linear mixed-effects) modeling will be used to analyse the dose concentration–time data of gantenerumab. Information from other clinical studies may be incorporated to establish the PK model. The selection of parameters and the derivation of individual measures of exposure, such as AUC, C_{max}, and trough serum concentration, will depend on the final PK model used for this analysis.

The influence of background medication on the pharmacokinetics of gantenerumab will be explored and, if appropriate, concentration–effect relationships may be assessed post hoc for PD, efficacy, or safety measures.

The results of this modeling analysis may be reported separately from the clinical study report.

CSF concentrations of gantenerumab may be tabulated and summarized as appropriate.

Prior to completion of the study a separate PK cutoff date may be established to allow expedient sample analyses and early access by third party vendors. The PK cutoff date will be applied when there is sufficient PK sample data available to adequately characterize PK.

Additional PK analyses will be conducted as appropriate and may be reported separately from the clinical study report.

6.7 INTERIM ANALYSIS

6.7.1 *Optional Futility* Analysis

The Sponsor may perform an interim analysis for futility approximately 116 weeks after 50% of the targeted study enrollment has been reached. If the study is extended by an additional 12 weeks, the interim analysis will be performed approximately 128 weeks after 50% of the targeted study enrollment has been reached. The exact timing of an interim analysis may be synchronized with Study WN29922.

An independent data coordinating center will be responsible for the interim analyses. The study results will only be reviewed by the iDMC and the Sponsor will remain blinded. *Other third party vendors may be involved in data preparation and analyses, as appropriate.*

The iDMC may recommend stop for futility if the failure criterion is met. The failure criterion will represent a low probability of a positive study outcome given the data observed at the time of interim analysis. *If the futility criteria are not met, the study continues beyond the interim analysis.* The failure criterion will be pre-specified in the iSAP.

In contrast, the iDMC may "declare the study positive for overwhelming efficacy" if the study meets the success criterion on the primary endpoint. The success criterion is defined as the p-value threshold determined by standard Lan and DeMets methodology (1983) for group sequential design using the O'Brien-Fleming boundary function. If the study continues beyond the interim analysis, the critical value at the final analysis will be adjusted accordingly.

Details of the futility analysis, including the final decision to conduct it, the rationale, timing, and statistical details for the analyses (such as the data that would be reviewed by the iDMC and futility thresholds) will be documented in the iSAP. This will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.

6.7.2 Optional Interim Analyses

Based on availability of information pertaining to gantenerumab or other compounds with similar mode of action that may emerge during the course of this study, the Sponsor may choose to conduct an additional interim analysis, *which may include efficacy, safety and biomarker outcomes including amyloid PET SUVr and/or other biomarkers to confirm PD effect. This analysis may be done on a whole study population or in a well predefined subgroup when approximately 50% of the overall population has reached*

Week 116. If the study is extended by an additional 12 weeks, the interim analysis will be performed once approximately 50% of the overall population has reached Week 128.

An independent data coordinating center will be responsible for the interim analyses. The study results will only be reviewed by the iDMC and the Sponsor will remain blinded. *Other third party vendors may be involved in data preparation and analyses, as appropriate.*

The iDMC may indicate that a pre-specified success criterion has been met. If so, the Sponsor may decide to present the data to a health authority. Any interim, unblinded data will be strictly firewalled to ensure those involved in the conduct of the ongoing trial and the WN42171 OLE trial remain fully blinded. If needed, appropriate measures will be taken to control the overall Type I error rate and described in the SAP.

Details of the interim analyses, including the decision to conduct the optional interim analyses, the rationale, timing, and statistical details for the analyses (such as the data that would be reviewed by the iDMC and efficacy thresholds) will be documented in an iSAP, and the iSAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.

6.8 CHINA EXTENSION ANALYSIS

The objective of the China extension and the China subpopulation analyses is to assess the treatment effects of gantenerumab in a population of participants enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA and to investigate the consistency in treatment effect between the China subpopulation and the global population for the purpose of registration in China.

All participants enrolled in the global enrollment phase in China will be included in the primary analysis. The analysis of the China extension will be conducted after the end of China extension and will be reported separately from the primary analysis and at a subsequent point in time. Details will be provided in the SAP.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. All electronic data from external vendors

will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

COA data will be collected through the use of an electronic device (tablet) provided by a vendor. Some COA data may be audio recorded for quality assurance purposes. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR, Part 11). The electronic data are available for view access only via secure access to an online Web portal. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive participant data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC CLINICAL OUTCOME DATA

Participants, study partners, and appropriate site staff will use an electronic device (tablet) to capture COA. For some COA, audio recordings may be used for quality assurance purposes. All data will be transmitted via Web automatically after entry into a centralized database maintained by the electronic device vendor.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive participant data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participant-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic COA data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of

time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Home Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each participant the objectives, methods, and potential risks associated with each optional procedure. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a participant's agreement to participate in optional procedures. Participants who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the participant or the participant's legally authorized representative before his or her participation in the study. The case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the participant to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Participants must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the participant or the participant's legally authorized representative. All signed and dated Consent Forms must remain in each participant's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include participant authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for participant authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the participant, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health

authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each participant enrolled in the study through assignment of a unique participant identification number. This means that participant names are not included in data sets that are transmitted to any Sponsor location.

Participant medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Medical information may be given to a participant's personal physician or other appropriate medical personnel responsible for the participant's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the participant data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/EC in accordance with established

IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

The overall procedures for quality assurance of clinical study data are described in the Roche standard operating procedures. This study will be sponsored by F. Hoffmann-La Roche Ltd. Roche will provide clinical operations oversight, site monitoring and management, data management support, and medical monitoring.

Study drug distribution may occur through an IxRS (see Section 4.2). Central facilities may be used for study assessments (i.e., ECG, lumbar puncture, specified laboratory tests, PK, rating scales, and MRI and PET imaging, as applicable).

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in participants involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in participants involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to participants or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

Table 1: Week –12 to Week 32; Dose Escalation with Q4W Administration

Assessment/Procedure	Prescreen & Screening	Baseline	Dose Escalation Period									Unsched Visit
	Weeks –12 to –1	Day 1	Day 4	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	
Dose Number		1 [a]		2	3	4	5 [b]	6 [b]	7 [a]	8 [b]	9 [b]	
Dose level in milligrams (mg)		120		120	120	255	255	255	510	510	510	
Informed consent(s) [c]	x											
Review of inclusion and exclusion criteria	x	B										
Medical history, personal status, and demographics	x											
Weight and height [t]	x	x							x			x
Clinical genotyping samples	x											
Clinical RNA samples	x											
Urinalysis [d]	x											
Urine sample for drugs of abuse [e]	x											
Coagulation (PT)	x											
Viral serology (HIV, hepatitis B, and hepatitis C)	x											
FCSRT	P [f]											
12-Lead electrocardiogram [g]	x	B				B			B			x
PK plasma sample [h, v]		B	x						B			x
ADA sample		B							B			x
Serum chemistry [i] and hematology [j]	x	B							B			x
Plasma biomarker sample [u]	x								B			x
Complete physical examination (includes neurological systems) [k]	x											x

Appendix 1: Schedule of Activities (cont.)
Table 1: Week –12 to Week 32; Dose Escalation with Q4W Administration (cont.)

Assessment/Procedure	Prescreen & Screening	Baseline	Dose Escalation Period									Unsched Visit
	Weeks –12 to –1	Day 1	Day 4	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	
Dose Number		1 [a]		2	3	4	5 [b]	6 [b]	7 [a]	8 [b]	9 [b]	
Dose level in milligrams (mg)		120		120	120	255	255	255	510	510	510	
Limited physical examination [l]									B			x
MRI scan [m, n]	x [o]					B			B			x
CSF and matching serum sampling [m, p] or PET scan [m, p]	x											
CDR	P&SP	P&SP							P&SP			P&SP
ADAS-Cog13		P							P			P
Verbal Fluency Task		P							P			P
Coding		P							P			P
ADCS-ADL		SP							SP			SP
FAQ		SP							SP			SP
MMSE	P [f]	P							P			P
EQ-5D		SP							SP			SP
QoL-AD		P&SP							P&SP			P&SP
ZCI-AD		SP							SP			SP
RUD-Lite		SP							SP			SP
NPI-Q		SP							SP			SP
C-SSRS BL/SLV		P							P			P
Vital signs [q]	x	B	B	B	B	B	B	B	B	B	B	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [r]	x	B		B	B	B	B	B	B	B	B	x
Study drug administration [h, s]		x		x	x	x	x	x	x	x	x	

Appendix 1: Schedule of Activities (cont.)
Table 1: Week –12 to Week 32; Dose Escalation with Q4W Administration (cont.)

ADAS-Cog13=Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL=Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR=Clinical Dementia Rating; CSF=cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D=EuroQol-Five Dimensions; FAQ=Functional Activities Questionnaire; FCSRT=Free and Cued Selective Reminding Test; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; NPI-Q=Neuropsychiatric Inventory–Questionnaire; PET=positron emission tomography; PK=pharmacokinetic; Prescreen=prescreening; Q4W=every 4 weeks; QoL-AD=Quality of Life–Alzheimer's Disease; RBR=Research Biosample Repository; RUD-Lite=Resource Utilization in Dementia–Lite; SC=subcutaneous; Unsched=unscheduled; Wk=week; ZCI-AD=Zarit Caregiver Interview–Alzheimer's Disease.

B=before study drug administration; P=participant completion; P&SP=participant and study partner completion; SP=study partner completion.

Notes: The visit window is ±7 days for dosing days and +3 days for non-dosing Day 4. For Q4W injections, the recommended minimum time between doses is 3 weeks. The maximum recommended time between doses should not exceed 6 weeks. Participants should return to initial planned schedule per randomization for subsequent visits.

In case of rescreening a participant, all screening assessments must be repeated other than the lumbar puncture and amyloid PET testing if performed within the previous 12 months for this study and are within the eligible ranges. In addition, clinical genotyping will not need to be repeated in case of rescreening.

[a] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first, and within 1 week prior to the first dose at baseline. All safety assessments (e.g., vital signs, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit time points stipulated in the schedule of activities. However, in exceptional circumstances, for post-randomization visits, if the caregiver, the primary rater or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.

[b] Visit suitable for home administration of gantenerumab.

[c] Participants in the optional prescreening period must provide written consent before any study-specific prescreening assessments are performed. If participant is eligible and decides to participate in the screening assessments, he or she will need to provide new written consent.

[d] Performed at the site by dipstick for blood, protein, glucose, and pH.

[e] Urine samples will be analyzed for the presence of the following drugs: amphetamine, benzodiazepines, cannabinoids, opiates, cocaine, barbiturates, and methadone.

[f] Can be done at prescreening or at screening. There is no need to repeat the test at screening if performed at prescreening.

[g] Electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the participant has been resting in a supine position for at least 5 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws, brain MRI scans, and lumbar puncture). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

[h] Accurate recording of the date and time of study drug administration and PK sampling is critical.

[i] Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). During the screening period (Week –1 to Week –12), hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[j] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelets, basophils, eosinophils, lymphocytes, monocytes, neutrophils, and WBC–other total counts.

[k] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

[l] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[m] CSF and matching serum sampling, and PET and MRI scans at screening should be performed once all other screening results are available and none exclude the participant from the study.

[n] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. It is not recommended that the MRI be performed on the same day as the IMP administration (especially during uptitration period during which it is recommended to do the MRI at least 10 days after the third dose of sing step). MRI should be performed before or at least 3 days following a lumbar puncture.

[o] Includes resting-state functional MRI and DTI outcome measures where available.

[p] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters. For post-baseline visits, lumbar puncture as well as serum sampling should be performed prior to dosing. Only one method (CSF or PET) confirming amyloid is necessary for all participants.

[q] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[r] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[s] Study drug administration should be performed only after all assessments/rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by SC injection. Participants should be observed up to 2 hours after dosing. After the fourth injection visit, the observation time may be reduced to 1 hour. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[t] Height measured at screening only.

[u] A plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

[v] A plasma PK sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

Appendix 1
Schedule of Activities (cont.)

Table 2: Week 36 to the End of Study: 510 mg Q2W

												Only for Participants Who Have Completed Week 104 when *the 12 week study extension* is Implemented			
	Treatment Period										Final Efficacy and Safety Assessments	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
Assessment/Procedure	Wk 36	Wk 38	Wk 40	Wk 41	Wk 42–50	Wk 52	Wk 54–74	Wk 76	Wk 78–102	Wk 103	Wk 104 [a, b]	Wk 116	Wk 152		
Dose number	10	11	12		13–17 [c]	18 [a]	19–29 [c]	30 [a]	31–43 [c]						
Dose level in milligrams (mg)	510	510	510		510	510	510	510	510						
12-Lead ECG						B		B			x	x		x	x
PK plasma sample [d]				x (Site visit)		B		B		x (Site visit)		x	x	x	x
ADA sample						B		B				x	x	x	x
Clinical RNA sample											x			x	
Serum chemistry [e] and hematology [f]						B		B			x	x	x	x	x
Plasma biomarker sample [o]						B					x			x	x
Complete physical examination (including neurological systems) [g]											x			x	x
Limited physical examination [h]						B		B							x
Weight						x		x			x	x	x	x	x

Appendix 1: Schedule of Activities (cont.)
Table 2: Week 36 to the End of Study: 510 mg Q2W (cont.)

												Only for Participants Who Have Completed Week 104 when *the 12 week study extension* is Implemented			
	Treatment Period										Final Efficacy and Safety Assessments	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
Assessment/Procedure	Wk 36	Wk 38	Wk 40	Wk 41	Wk 42–50	Wk 52	Wk 54–74	Wk 76	Wk 78–102	Wk 103	Wk 104 [a, b]	Wk 116	Wk 152		
Dose number	10	11	12		13–17 [c]	18 [a]	19–29 [c]	30 [a]	31–43 [c]						
Dose level in milligrams (mg)	510	510	510		510	510	510	510	510						
MRI scan [i]	B				Wk 48 [j]		Wk 60	B			x [j]			x [j]	x
CSF [k] and matching serum sampling (for participants enrolled based on CSF eligibility criteria only)								x			x			x [k]	
CDR						P&SP		P&SP			P&SP		P&SP	P&SP	P&SP
ADAS-Cog13						P		P			P		P	P	P
Verbal Fluency Task						P		P			P		P	P	P
Coding						P		P			P		P	P	P
ADCS-ADL						SP		SP			SP		SP	SP	SP
FAQ						SP		SP			SP		SP	SP	SP
MMSE						P		P			P		P	P	P
EQ-5D						SP		SP			SP			SP	SP
QOL-AD						P&SP		P&SP			P&SP			P&SP	P&SP
ZCI-AD						SP		SP			SP			SP	SP
RUD-Lite						SP		SP			SP			SP	SP

Appendix 1: Schedule of Activities (cont.)
Table 2: Week 36 to the End of Study: 510 mg Q2W (cont.)

												Only for Participants Who Have Completed Week 104 when *the 12 week study extension* is Implemented			
	Treatment Period										Final Efficacy and Safety Assessments	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
Assessment/Procedure	Wk 36	Wk 38	Wk 40	Wk 41	Wk 42–50	Wk 52	Wk 54–74	Wk 76	Wk 78–102	Wk 103	Wk 104 [a, b]	Wk 116	Wk 152		
Dose number	10	11	12		13–17 [c]	18 [a]	19–29 [c]	30 [a]	31–43 [c]						
Dose level in milligrams (mg)	510	510	510		510	510	510	510	510						
NPI-Q						SP		SP			SP			SP	SP
C-SSRS BL/SLV						P		P			P			P	P
Vital signs [l]	B	B	B		B	B	B	B	B		x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [m]	B	B	B		B	B	B	B	B		x	x		x	x
Study drug administration [d, n]	x	x	x		x	x	x	x	x						

ADAS-Cog13=Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL=Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR=Clinical Dementia Rating; CSF=cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D=EuroQol-Five Dimensions; FAQ=Functional Activities Questionnaire; FCSRT=Free and Cued Selective Reminding Test; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; NPI-Q=Neuropsychiatric Inventory–Questionnaire; OLE=open-label extension; PET=positron emission tomography; PK=pharmacokinetic; Q2W=every 2 weeks; QoL-AD=Quality of Life–Alzheimer's Disease; RBR=Research Biosample Repository; RUD-Lite=Resource Utilization in Dementia–Lite; SC=subcutaneous; Unsched=unscheduled; Wk=week; ZCI-AD=Zarit Caregiver Interview–Alzheimer's Disease.

B=before study drug administration; P=participant completion; P&SP=participant and study partner completion; SP=study partner.

Appendix 1: Schedule of Activities (cont.)
Table 2: Week 36 to the End of Study: 510 mg Q2W (cont.)

Notes: The visit window is ± 3 days for dosing days and +3 days for Week 41 and Week 103 non-dosing days. For Q2W injections, the recommendation is not to administer more than 1020 mg (i.e., 2 times 510 mg Q2W) within 28 days. Participants should return to initial planned schedule per randomization for subsequent visits.

[a] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vitals, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit time points stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.

[b] Transition to OLE study for participants who are eligible to participate.

[c] Visit suitable for home administration of gantenerumab.

[d] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria

[e] Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). At Week 52 and Week 104, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[f] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

[g] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary (optional), and neurological systems.

[h] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[i] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[j] Includes resting-state functional MRI and DTI outcome measures, where available.

[k] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For participants enrolling based on CSF eligibility criteria, CSF and matching serum samples are optional at Week 76. Lumbar puncture does not have to be performed the same day as the main Week 76 visit or Week 104 visit, but should be performed in a reasonable time around these visits. The need for CSF collection at early termination visit *should* be *determined* on a case-by-case basis, *based on the participant's condition and the time since last lumbar puncture and advice by the Medical Monitor may be sought.*

Appendix 1: Schedule of Activities (cont.)
Table 2: Week 36 to the End of Study: 510 mg Q2W (cont.)

[l] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[m] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[n] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by subcutaneous injection (full details are provided in the pharmacy manual). Participants should be observed for up to 2 hours after dosing. After the fourth injection visit, this observation time may be reduced to 1 hour. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[o] A plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

Appendix 1
Schedule of Activities (cont.)

Table 3: Scenario 1 / Week 104 to the End of Study: 510 mg Q2W

(3-Month Extension)

Assessment/Procedure	Treatment Period			Final Safety and Efficacy Assessment	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
	Wk 104 [a]	Wk 106-114 [c]	Wk 115	Wk 116 [a, b]	Wk 128	Wk 164		
Dose number	44	45-49						
Dose level in milligrams (mg)	510	510						
12-Lead ECG	x			x	x		x	x
PK plasma sample [d]			x (site visit)		x	x	x	x
ADA sample					x	x	x	x
Clinical RNA sample	x			x			x	
Serum chemistry [e] and hematology [f]	x			x	x	x	x	x
Plasma biomarker sample [o]	x			x			x	x
Complete physical examination (including neurological systems) [g]				x			x	x
Limited physical examination [h]	x							x
Weight	x			x	x	x	x	x
MRI scan [i]	x [j]			x [j]			x [j]	x

Appendix 1: Schedule of Activities (cont.)

Table 3: Scenario 1 / Week 104 to the End of Study: 510 mg Q2W (3-Month Extension)

Assessment/Procedure	Treatment Period			Final Safety and Efficacy Assessment	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
	Wk 104 [a]	Wk 106-114 [c]	Wk 115	Wk 116 [a, b]	Wk 128	Wk 164		
Dose number	44	45-49						
Dose level in milligrams (mg)	510	510						
CSF [k] and matching serum sampling (for participants enrolled based on CSF eligibility criteria only)				x			x [k]	
CDR	P&SP			P&SP		P&SP	P&SP	P&SP
ADAS-Cog13	P			P		P	P	P
Verbal Fluency Task	P			P		P	P	P
Coding	P			P		P	P	P
ADCS-ADL	SP			SP		SP	SP	SP
FAQ	SP			SP		SP	SP	SP
MMSE	P			P		P	P	P
EQ-5D	SP			SP			SP	SP
QOL-AD	P&SP			P&SP			P&SP	P&SP
ZCI-AD	SP			SP			SP	SP
RUD-Lite	SP			SP			SP	SP
NPI-Q	SP			SP			SP	SP
C-SSRS BL/SLV	P			P			P	P
Vital signs [l]	x	x		x	x	x	x	x
Concomitant medications	x	x		x	x	x	x	x
Adverse events	x	x		x	x	x	x	x
Urine pregnancy test [m]	x	x		x	x		x	x
Study drug administration [d, n]	x	x						

Appendix 1: Schedule of Activities (cont.)

Table 3: Scenario 1 / Week 104 to the End of Study: 510 mg Q2W (3-Month Extension)

ADAS-Cog13=Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL=Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR=Clinical Dementia Rating; CSF=cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D=EuroQol-Five Dimensions; FAQ=Functional Activities Questionnaire; FCSRT=Free and Cued Selective Reminding Test; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; NPI-Q=Neuropsychiatric Inventory–Questionnaire; OLE=open-label extension; PET=positron emission tomography; PK=pharmacokinetic; Q2W=every 2 weeks; QoL-AD=Quality of Life–Alzheimer's Disease; RBR=Research Biosample Repository; RUD-Lite=Resource Utilization in Dementia–Lite; SC=subcutaneous; Unsched=unscheduled; Wk=week; ZCI-AD=Zarit Caregiver Interview–Alzheimer's Disease.

B=before study drug administration; P=participant completion; P&SP=participant and study partner completion; SP=study partner.

Notes: The visit window is ± 3 days for dosing days and +3 days for Week 115 non-dosing days. For Q2W injections, the recommendation is not to administer more than 1020 mg (i.e., 2 times 510 mg Q2W) within 28 days. Participants should return to initial planned schedule per randomization for subsequent visits.

SoA from Week −12 to Week 103 for scenario 1 is described in Appendix 1, Table 1 and Table 2.

[a] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vitals, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit time points stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.

[b] Transition to OLE study for participants who are eligible to participate.

[c] Visit suitable for home administration of gantenerumab.

[d] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

[e] Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). At Week 104 and Week 116, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[f] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

[g] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

[h] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[i] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[j] Includes resting-state functional MRI and DTI outcome measures, where available.

[k] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For participants enrolling based on CSF eligibility criteria, CSF and matching serum samples are optional at Week 76 ; lumbar

puncture does not have to be performed the day of Week 76 or Week 116 visit, but should be performed in a reasonable time around these visits; the need of CSF collection at early termination visit *should* be *determined* on a case-by-case basis, *based on the participant's condition and the time since last lumbar puncture and advice by the Medical Monitor may be sought*.

[l] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[m] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[n] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by subcutaneous injection (full details are provided in the pharmacy manual). Participants should be observed for about 1 hour after dosing. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[o] A plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria

Appendix 1
Schedule of Activities (cont.)

Table 4: Scenario 2 / Week 104 to the End of Study: 510 mg Q2W (Additional 3-Month Extension)

Assessment/Procedure	Treatment Period			Final Safety and Efficacy Assessment	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
	Wk 104[a]	Wk 106-126[c]	Wk 127	Wk 128[a, b]	Wk 140	Wk 176		
Dose number	44	45-55						
Dose level in milligrams (mg)	510	510						
12-Lead ECG	x			x	x		x	x
PK plasma sample [d]			x (site visit)		x	x	x	x
ADA sample					x	x	x	x
Clinical RNA sample	x			x			x	
Serum chemistry [e] and hematology [f]	x			x	x	x	x	x
Plasma biomarker sample [o]	x			x			x	x
Complete physical examination (including neurological systems) [g]				x			x	x
Limited physical examination [h]	x							x
Weight	x			x	x	x	x	x
MRI scan [i]	x [j]			x [j]			x [j]	x
CSF [k] and matching serum sampling (for participants enrolled based on CSF eligibility criteria only)				x			x [k]	
CDR	P&SP			P&SP		P&SP	P&SP	P&SP
ADAS-Cog13	P			P		P	P	P

Appendix 1: Schedule of Activities (cont.)
Table 4: Scenario 2 Only Week 104 to the End of Study: 510 mg Q2W (Additional 3-Month Extension)

Assessment/Procedure	Treatment Period			Final Safety and Efficacy Assessment	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
	Wk 104[a]	Wk 106-126[c]	Wk 127	Wk 128[a, b]	Wk 140	Wk 176		
Dose number	44	45-55						
Dose level in milligrams (mg)	510	510						
Verbal Fluency Task	P			P		P	P	P
Coding	P			P		P	P	P
ADCS-ADL	SP			SP		SP	SP	SP
FAQ	SP			SP		SP	SP	SP
MMSE	P			P		P	P	P
EQ-5D	SP			SP			SP	SP
QOL-AD	P&SP			P&SP			P&SP	P&SP
ZCI-AD	SP			SP			SP	SP
RUD-Lite	SP			SP			SP	SP
NPI-Q	SP			SP			SP	SP
C-SSRS BL/SLV	P			P			P	P
Vital signs [l]	x	x		x	x	x	x	x
Concomitant medications	x	x		x	x	x	x	x
Adverse events	x	x		x	x	x	x	x
Urine pregnancy test [m]	x	x		x	x		x	x
Study drug administration [d, n]	x	x						

ADAS-Cog13=Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL=Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR=Clinical Dementia Rating; CSF=cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D=EuroQol-Five Dimensions; FAQ=Functional Activities Questionnaire; FCSRT=Free and Cued Selective Reminding Test; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; NPI-Q=Neuropsychiatric Inventory–Questionnaire; OLE=open-label extension; PET=positron emission tomography; PK=pharmacokinetic; Q2W=every 2 weeks; QoL-AD=Quality of Life–Alzheimer's Disease; RBR=Research Biosample Repository; RUD-Lite=Resource Utilization in Dementia–Lite; SC=subcutaneous; Unsched=unscheduled; Wk=week; ZCI-AD=Zarit Caregiver Interview–Alzheimer's Disease.

Appendix 1: Schedule of Activities (cont.)
Table 4: Scenario 2 Only Week 104 to the End of Study: 510 mg Q2W (Additional 3-Month Extension)

B = before study drug administration; P = participant completion; P&SP = participant and study partner completion; SP=study partner.

Notes: The visit window is ± 3 days for dosing days and + 3 days for Week 127 non-dosing days. For Q2W injections, the recommendation is not to administer more than 1020 mg (i.e., 2 times 510 mg Q2W) within 28 days. Participants should return to initial planned schedule per randomization for subsequent visits.

SoA from Week −12 to Week 103 for scenario 2 is described in Appendix 1, Table 1 and Table 2.

[a] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vitals, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit time points stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.

[b] Transition to OLE study for participants who are eligible to participate.

[c] Visit suitable for home administration of gantenerumab.

[d] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria

[e] Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). At Week 104 and Week 128, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[f] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

[g] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

[h] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[i] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[j] Includes resting-state functional MRI and DTI outcome measures, where available.

[k] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For participants enrolling based on CSF eligibility criteria, CSF and matching serum samples are optional at Week 76; lumbar puncture does not have to be performed the day of Week 76 or Week 128 visit, but should be performed in a reasonable time around these visits; the need of CSF collection at early termination visit *should* be *determined* on a case-by-case basis, *based on the participant's condition and the time since last lumbar puncture and advice by the Medical Monitor may be sought.*

[l] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

Appendix 1: Schedule of Activities (cont.)
Table 4: Scenario 2 Only Week 104 to the End of Study: 510 mg Q2W (Additional 3-Month Extension)

[m] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[n] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by subcutaneous injection (full details are provided in the pharmacy manual). Participants should be observed for about 1 hour after dosing. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[o] A plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria

Appendix 1
Schedule of Activities (cont.)

Table 5: Schedule of Activities (OLE Day 1 to Week 22: Dose Escalation with Q2W Administration)

Assessment/Procedure	Open-Label Extension Treatment Period													OLE Early Term Visit [m]	OLE UV
	OLE Day 1	OLE Day 4	OLE Wk 2	OLE Wk 4	OLE Wk 6	OLE Wk 8	OLE Wk 10	OLE Wk 12	OLE Wk 14	OLE Wk 16	OLE Wk 18	OLE Wk 20	OLE Wk 22		
Dose number	1[a]		2	3	4	5	6	7	8	9 [b]	10 [b]	11 [b]	12 [b]		
Dose level in milligrams (mg) for participants previously on placebo	120			120		120		255		255		255			
Dose level in milligrams (mg) for participants previously on active	510		510	510	510	510	510	510	510	510	510	510	510		
Informed consent(s)	x														
Review of inclusion and exclusion criteria	x														
Weight														x	x
12-Lead electrocardiogram								B						x	x
PK Plasma Sample [c]	x	x												*x*	x
ADA sample	x													x	x
Serum chemistry [d] and hematology [e]														x	x

Appendix 1: Schedule of Activities (cont.)
Table 5: Schedule of Activities (OLE Day 1 to Week 22: Dose Escalation with Q2W Administration) (cont.)

Assessment/Procedure	Open-Label Extension Treatment Period													OLE Early Term Visit [m]	OLE UV
	OLE Day 1	OLE Day 4	OLE Wk 2	OLE Wk 4	OLE Wk 6	OLE Wk 8	OLE Wk 10	OLE Wk 12	OLE Wk 14	OLE Wk 16	OLE Wk 18	OLE Wk 20	OLE Wk 22		
Dose number	1[a]		2	3	4	5	6	7	8	9 [b]	10 [b]	11 [b]	12 [b]		
Dose level in milligrams (mg) for participants previously on placebo	120			120		120		255		255		255			
Dose level in milligrams (mg) for participants previously on active	510		510	510	510	510	510	510	510	510	510	510	510		
Plasma biomarker sample [l]														x	x
Complete physical examination (includes neurological systems) [f]														x	x
Limited physical examination [g]															x
MRI scan [h]								B						x [n]	x
CDR														P&SP	P&SP
ADAS-Cog 13														P	P
MMSE														P	P
Verbal Fluency Test														P	P
Coding														P	P
ADCS-ADL														SP	SP
FAQ														SP	SP
EQ-5D														SP	SP
QOL-AD														P&SP	P&SP
ZCI-AD														SP	SP

Appendix 1: Schedule of Activities (cont.)
Table 5: Schedule of Activities (OLE Day 1 to Week 22: Dose Escalation with Q2W Administration) (cont.)

Assessment/Procedure	Open-Label Extension Treatment Period													OLE Early Term Visit [m]	OLE UV
	OLE Day 1	OLE Day 4	OLE Wk 2	OLE Wk 4	OLE Wk 6	OLE Wk 8	OLE Wk 10	OLE Wk 12	OLE Wk 14	OLE Wk 16	OLE Wk 18	OLE Wk 20	OLE Wk 22		
Dose number	1[a]		2	3	4	5	6	7	8	9 [b]	10 [b]	11 [b]	12 [b]		
Dose level in milligrams (mg) for participants previously on placebo	120			120		120		255		255		255			
Dose level in milligrams (mg) for participants previously on active	510		510	510	510	510	510	510	510	510	510	510	510		
RUD-Lite														SP	SP
NPI-Q														SP	SP
C-SSRS/SLV														P	P
CSF and matching serum sampling (for participants enrolled based on CSF eligibility criteria in double-blind part only)														x [o]	
Vital Signs [i]	B	x	B	B	B	B	B	B	B	B	B	B	B	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [i]	B		B	B	B	B	B	B	B	B	B	B	B	x	x
Study drug administration [c, k]	x		x	x	x	x	x	x	x	x	x	x	x		

ADAS-Cog13= Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR = Clinical Dementia Rating; CSF = cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; FCSRT= Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; OLE=open-label extension; PET = positron emission

tomography; PK = pharmacokinetic; Q2W = every 2 weeks; QoL-AD = Quality of Life–Alzheimer's Disease; RBR = Research Biosample Repository; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; UV = unscheduled visit; Wk = week; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

B = before study drug administration; P = participant completion; P&SP= participant and study partner completion; SP=study partner.

Notes: The visit window is ± 3 days for dosing days and +3 days for OLE non-dosing Day 4. Participants should return to initial planned schedule per randomization for subsequent visits.

[a] OLE Day 1 dosing should take place approximately 2 weeks after final efficacy visit has been completed.

[b] Visit suitable for home administration of gantenerumab.

[c] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria

[d] Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). At early termination, hemoglobin A1C, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[e] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

[f] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

[g] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[h] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[i] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[j] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[k] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by subcutaneous injection (full details are provided in the pharmacy manual). Participants should be observed for up to 2 hours after dosing. After the 8th injection visit, this observation time may be reduced to 1 hour. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[l] A plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria

[m] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vitals, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit time points stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater or even the participant cannot perform these assessments as per schedule of activities they may be performed up to 4 weeks out of window.

[n] Includes resting-state functional MRI and DTI outcome measures, where available.

[o] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For patients enrolling based on CSF eligibility criteria, the need of CSF collection at early termination visit during OLE *should* be *determined* on a case-by-case basis, *based on the participant's condition and the time since last lumbar puncture and advice by the Medical Monitor may be sought.*

Appendix 1
Schedule of Activities (cont.)

Table 6: Schedule of Activities (OLE Week 24 to Week 35: Dose Escalation with Q2W Administration)

Assessment/Procedure	Open-Label Extension Treatment Period							Follow-up Period for Participants Not Enrolling in Study WN42171		OLE Early Term Visit [a]	OLE Unsched Visit
	OLE Wk 24	OLE Wk 26	OLE Wk 28	OLE Wk 30	OLE Wk 32	OLE Wk 34	OLE Wk 35	OLE Follow Up 1	OLE Follow Up 2		
Dose number	13 [a]	14 [b]	15 [b]	16 [b]	17 [b]	18 [b]					
Dose level in milligrams (mg) for participants previously on placebo	510		510		510						
Dose level in milligrams (mg) for participants previously on active	510	510	510	510	510	510					
Informed consent(s)											
Review of inclusion and exclusion criteria											
Weight	x							x	x	x	x
12-Lead electrocardiogram	x							x		x	x
PK plasma sample [c]	x							x	x	*x*	*x*
ADA sample	x							x	x	x	x
Serum chemistry [d] and hematology [e]	x							x	x	x	x
Plasma biomarker sample [n]	x									x	x
Complete physical examination (includes neurological systems) [f]										x	x
Limited physical examination [g]	x										x

Appendix 1: Schedule of Activities (cont.)
Table 6: Schedule of Activities (OLE Week 24 to Week 35: Dose Escalation with Q2W Administration) (cont.)

Assessment/Procedure	Open-Label Extension Treatment Period							Follow-up Period for Participants Not Enrolling in Study WN42171		OLE Early Term Visit [a]	OLE Unsched Visit
	OLE Wk 24	OLE Wk 26	OLE Wk 28	OLE Wk 30	OLE Wk 32	OLE Wk 34	OLE Wk 35	OLE Follow Up 1	OLE Follow Up 2		
Dose number	13 [a]	14 [b]	15 [b]	16 [b]	17 [b]	18 [b]					
Dose level in milligrams (mg) for participants previously on placebo	510		510		510						
Dose level in milligrams (mg) for participants previously on active	510	510	510	510	510	510					
MRI scan [h]	B						x			x[i]	x
CDR	P&SP								P&SP	P&SP	P&SP
ADAS-Cog 13	P								P	P	P
MMSE	P								P	P	P
Verbal Fluency Test	P								P	P	P
Coding	P								P	P	P
ADCS-ADL	SP								SP	SP	SP
FAQ	SP								SP	SP	SP
EQ-5D	SP								SP	SP	SP
QOL-AD	P&SP								P&SP	P&SP	P&SP
ZCI-AD	SP								SP	SP	SP
RUD-Lite	SP								SP	SP	SP
NPI-Q	SP								SP	SP	SP
C-SSRS/SLV	P								P	P	P

Appendix 1: Schedule of Activities (cont.)
Table 6: Schedule of Activities (OLE Week 24 to Week 35: Dose Escalation with Q2W Administration) (cont.)

Assessment/Procedure	Open-Label Extension Treatment Period							Follow-up Period for Participants Not Enrolling in Study WN42171		OLE Early Term Visit [a]	OLE Unsched Visit
	OLE Wk 24	OLE Wk 26	OLE Wk 28	OLE Wk 30	OLE Wk 32	OLE Wk 34	OLE Wk 35	OLE Follow Up 1	OLE Follow Up 2		
Dose number	13 [a]	14 [b]	15 [b]	16 [b]	17 [b]	18 [b]					
Dose level in milligrams (mg) for participants previously on placebo	510		510		510						
Dose level in milligrams (mg) for participants previously on active	510	510	510	510	510	510					
CSF and matching serum sampling (for participants enrolled based on CSF eligibility criteria in double-blind part only)										x [j]	
Vital signs [k]	B	B	B	B	B	B		x	x	x	x
Concomitant medications	x	x	x	x	x	x		x	x	x	x
Adverse events	x	x	x	x	x	x		x	x	x	x
Urine pregnancy test [l]	B	B	B	B	B	B		x		x	x
Study drug administration [c, m]	x	x	x	x	x	x					

ADAS-Cog13= Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR = Clinical Dementia Rating; CSF = cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; FCSRT= Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; OLE=open-label extension; PET = positron emission tomography; PK = pharmacokinetic; Q2W = every 2 weeks; QoL-AD = Quality of Life–Alzheimer's Disease; RBR = Research Biosample Repository; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; Unsched = unscheduled; Wk = week; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

B = before study drug administration; P = participant completion; P&SP= participant and study partner completion; SP=study partner.

Appendix 1: Schedule of Activities (cont.)
Table 6: Schedule of Activities (OLE Week 24 to Week 35: Dose Escalation with Q2W Administration) (cont.)

Notes: The visit window is ± 3 days for dosing days and +3 days for OLE non-dosing Day 4. Participants should return to initial planned schedule per randomization for subsequent visits.

[a] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vitals, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit time points stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater or even the participant cannot perform these assessments as per schedule of activities they may be performed up to 4 weeks out of window.

[b] Visit suitable for home administration of gantenerumab.

[c] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

[d] Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). At early termination, hemoglobin A1C, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[e] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

[f] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

[g] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[h] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[i] Includes resting-state functional MRI and DTI outcome measures, where available.

[j] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For participants enrolling based on CSF eligibility criteria, the need of CSF collection at early termination visit during OLE *should* be *determined* on a case-by-case basis, *based on the participant's condition and the time since last lumbar puncture and advice by the Medical Monitor may be sought.*

[k] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[l] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[m] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by subcutaneous injection (full details are provided in the pharmacy manual). Participants should be observed for up to 2 hours after dosing. After the 8th injection visit, this observation time may be reduced to 1 hour. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[n] A plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

Appendix 2
National Institute on Aging/Alzheimer's Association Criteria for Mild Alzheimer's Disease

NIA/AA Category	Description
Probable dementia: core clinical criteria Meets criteria for dementia described earlier in the text, and, in addition, has the following characteristics:	A. Insidious onset: Symptoms have a gradual onset over months to years, not sudden over hours or days B. Clear-cut history of worsening of cognition by report or observation; and C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories: 1. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text. 2. Non-amnestic presentations • Language presentation: The most prominent deficits are in word finding, but deficits in other cognitive domains should be present. • Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present. • Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present. D. The diagnosis of probable AD dementia should not be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or non-fluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

Appendix 2: National Institute on Aging/Alzheimer's Association Criteria for Mild Alzheimer's Disease (cont.)

NIA/AA Category	Description
Probable AD dementia with increased level of certainty	**Probable AD dementia with documented decline** In persons who meet the core clinical criteria for probable AD dementia, documented cognitive decline increases the certainty that the condition represents an active, evolving pathologic process, but it does not specifically increase the certainty that the process is that of AD pathophysiology. Probable AD dementia with documented decline is defined as follows: evidence of progressive cognitive decline on subsequent evaluations based on information from informants and cognitive testing in the context of either formal neuropsychological evaluation or standardized mental status examinations. **Probable AD dementia in a carrier of a causative AD genetic mutation** In persons who meet the core clinical criteria for probable AD dementia, evidence of a causative genetic mutation (in APP, PSEN1, or PSEN2) increases the certainty that the condition is caused by AD pathology. The working group noted that carriage of the ε4 allele of the *APOE* gene was not sufficiently specific to be considered in this category.
Probable AD dementia with evidence of the AD pathophysiological process	AD dementia is part of a continuum of clinical and biological phenomena. AD dementia is fundamentally a clinical diagnosis. To make a diagnosis of AD dementia with biomarker support, the core clinical diagnosis of AD dementia must first be satisfied. Relevant biomarkers include amyloid-β (CSF or PET) and tau (CSF or PET).

AD = Alzheimer's disease; *APOE* = apolipoprotein E; CSF = cerebral spinal fluid; NIA/AA = National Institute on Aging/Alzheimer's Association; PET = positron emission tomography.

REFERENCE

McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:263–9.

Appendix 3
National Institute on Aging/Alzheimer's Association Criteria for Prodromal Alzheimer's Disease (Mild Cognitive Impairment due to Alzheimer's Disease)

NIA/AA Category	Clinical and Cognitive Criteria
Clinical criteria	• Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time) • Objective evidence of impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains) • Preservation of independence in functional abilities • Not demented
Etiology of MCI consistent with AD pathophysiological process	• Rule out vascular, traumatic, medical causes of cognitive decline, when possible • Provide evidence of longitudinal decline in cognition, when feasible • Report history consistent with AD genetic factors, when relevant
Prodromal AD dementia with evidence of the AD pathophysiological process	Prodromal AD is part of a continuum of clinical and biological phenomena. Prodromal AD is fundamentally a clinical diagnosis. To make a diagnosis of prodromal AD with biomarker support, the core clinical diagnosis of prodromal AD must first be satisfied. Relevant biomarkers include amyloid-β (CSF or PET) and tau (CSF or PET).

AD = Alzheimer's disease; CSF = cerebral spinal fluid; MCI = mild cognitive impairment; NIA/AA = National Institute on Aging/Alzheimer's Association; PET = positron emission tomography.

REFERENCES

Albert MS, DeKosky ST, Dickson B, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270–9.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data

The population pharmacokinetic positron emission tomography (PK-PET) response analysis of the gantenerumab Phase III study WN25203 data and aducanumab Phase Ib PET study model was built using pooled information from the gantenerumab Phase III study WN25203 and the aducanumab Phase Ib PRIME study. Details about how this population analysis was conducted and evaluated are provided herein.

1. MATERIALS AND METHODS

1.1 MODELING HYPOTHESIS

Based on the high degree of similarity between gantenerumab and aducanumab, it was assumed that both compounds share the same PK properties in terms of disposition, metabolism, elimination, and the same relationship between in serum concentrations and reduction in standardized uptake value ratio (SUVr) amyloid PET.

It was also assumed that the SUVr data from aducanumab and gantenerumab could be pooled given that they were derived using the same whole cerebellum reference region and that the sensorimotor region used only in the composite SUVr of aducanumab was having little effect on the SUVr values.

1.2 PHARMACOKINETIC AND PHARMCODYNAMIC DATA

A PK-pharmacodynamic (PD) dataset for PET model was built using information from the Phase III gantenerumab study (WN25203) together with information from Phase Ib aducanumab trial (PRIME).

2.2.1 Gantenerumab PK and PET Data

2.2.1.1 PK Information

Each patient participating in Study WN25203 provided samples for measurement of their PK serum concentrations at the following scheduled timepoints: Weeks 1, 8, 20, 44, 53, 68, 100, and 101.

The PK data from Study WN25203 were analysed using a population PK model that was previously developed on the basis of Phase I studies.

The Phase I PK database comprised data from 235 patients and healthy volunteers for a total of 4082 PK observations. It contained data from both IV and SC administration, single and multiple repeated doses administered every 4 weeks (Q4W), with dose values ranging for the repeated dose administrations from 6 mg to 200 mg for the IV, 105 and 225 mg for the SC, and up to 300 mg SC and 400 mg IV when administered

once. A two-compartment model with a 0 order followed by first-order absorption best described the Phase I data. Population parameter values are reported in Table 1.

Table 1 Population PK Parameters Estimated from Phase I Study Data

Parameter	Mean	RSE%	BSV%	RSE%
CL (L/day)	0.336	3.20%	26.1%	6.9%
V2 (L)	3.52	5.60%	31.3%	18.5%
Q (L/day)	0.869	9.50%	55.5%	10.6%
V3 (L)	6.38	4.10%	24.9%	10%
KA (/day)	0.22	8.90%	52.2%	21.1%
D1 (/day)	0.0821	7.10%	96.6%	8.9%
F1 (–)	0.494	3.90%	42.8%	10.5%
PROP.ERR	0.196	5.40%		
ADD.ERR (μg/mL)	0.0121	21.70%		

ADD_ERR = additional error; CL=clearance; D1 = zero order rate constant; F1 = absolute bioavailability; KA = absorption rate constant; KeO = rate constant for drug transfer from serum to effect compartment; PK = pharmacokinetic; POW = power; PROP_ERR = proportional error; Q = intercompartmental clearance; RSE = relative standard error; SLOP = slope; V2 = central compartment; V3 = peripheral volume 3.

The population PK model was used to perform an empirical Bayesian analysis in non-linear mixed-effects model (NONMEM) of the PK data collected from Study WN25203 and to derive for each patient the individual PK parameters, as well as an estimation of the individual average concentrations over the period of observation.

2.2.1.2 PET Information

Among the 799 patients enrolled in Study WN25203, 114 patients participated in the amyloid PET substudy (using the AV-45 ligand). Scans were performed at baseline, Weeks 20, 60, and 100. For patients entering the 2-year, double-blinded portion of the trial (Part 2), another scan was obtained at Week 156.

PET data up to Week 100 (inclusive) were considered for the PK-PD modeling investigations, and the PET database comprised a total of 348 SUVr observations determined using the whole cerebellum as the reference region.

2.2.2 Aducanumab PK and PET PD Data

Aducanumab PK and PET data were extracted from a poster (n°ADPD5–2113) and from slides that were presented at the 12th International Congress on Alzheimer's Disease and Parkinson's Disease (ADPD) in March 2015 in Nice, France.

The aducanumab data were collected in the Phase Ib, randomized, double-blind, placebo-controlled study (PRIME) in patients with prodromal or mild Alzheimer's

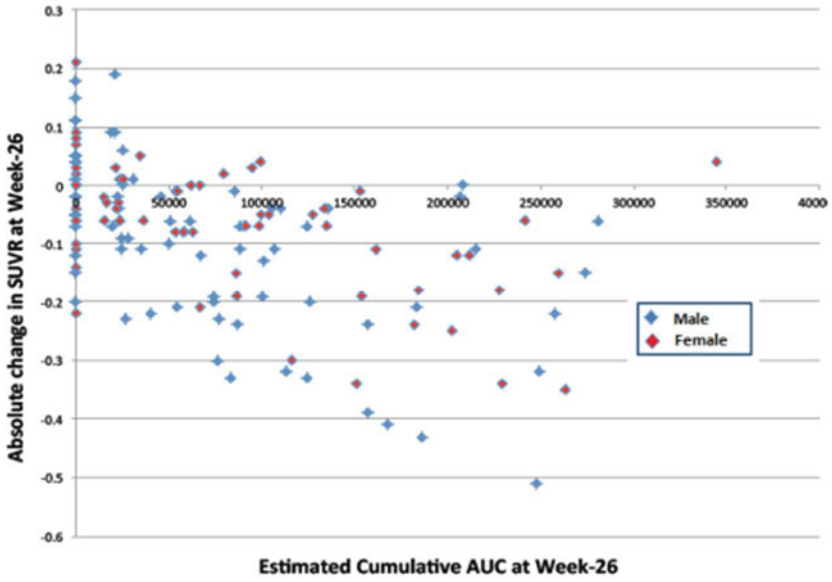
disease. The study design involved a parallel-group design, with a 54-week treatment period. Patients received 14 IV infusions of aducanumab Q4W; four dose groups were evaluated, including the placebo group, and included the 1-mg/kg, 3-mg/kg, 6-mg/kg, and 10-mg/kg dose groups, respectively. SUVr measurements were performed at baseline, Week 26, and Week 54 and were determined using the whole cerebellum as the reference region.

The following figures were used from the aducanumab poster and slides:

- A figure displaying the individual absolute change in SUVr at Week 26 in function of the individual cumulative area under the concentration-time curve (AUC) at Week 26 (see Figure 1)
- A table presenting the time course of the mean SUVr up to Week 54 by dose group (see Table 2)
- A figure displaying the relationship between the individual cumulative AUC at Week 26 and the four doses investigated in the PRIME study (see Figure 2)

The individual data, as depicted in Figure 1, were extracted and a database of 123 patients with their respective cumulative AUC values at Week 26 and the absolute change from baseline in SUVr. The mean data from Figure 2 were used to extrapolate the individual aducanumab PET data at Weeks 26 to 54 and, also, to assign a mean SUVr baseline value to each aducanumab dose group. In addition, the data from Figure 2 were used to determine from which dose group the individual cumulative AUC values at Week 26 from Figure 1 were most likely derived.

Figure 1 Individual Absolute Change in SUVr Observed in Aducanumab Data at Week 26 with Respect to Cumulative Exposure



AUC = area under the concentration–time curve; SUVr = standardized uptake value ratio.
Source: Hang et al. 2015.

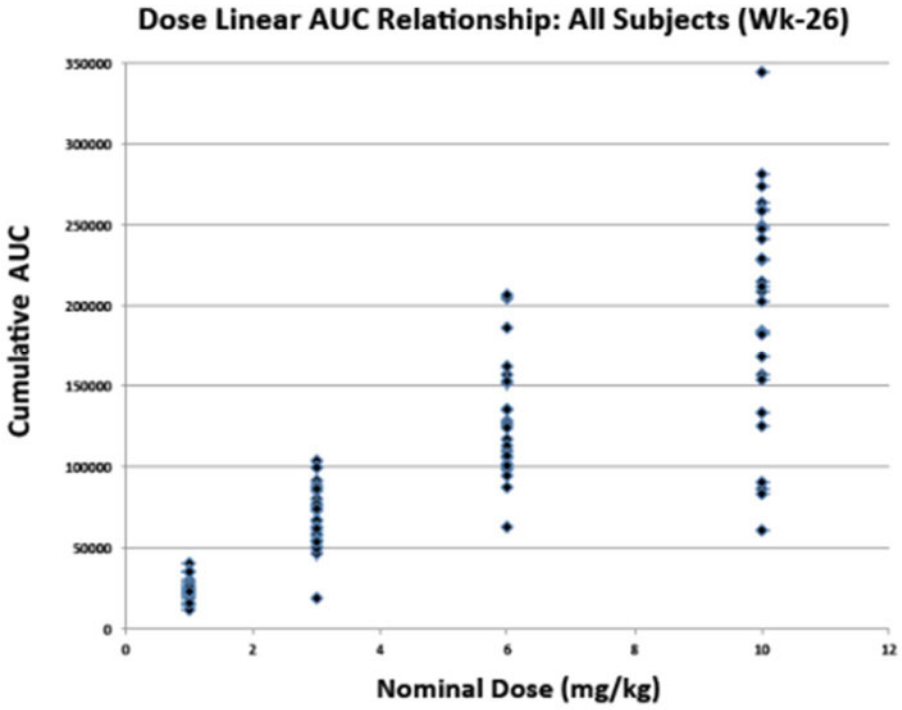
Table 2 Mean Composite PET SUVr Data Observed in the Aducanumab Phase Ib Trial (PRIME) per Dose Group, Using the Whole Cerebellum as Reference Region

	Observed Mean Composite SUVr		
Dose Group	Baseline	Week 26	Week 54
Placebo	1.45	1.42	1.42
1 mg/kg	1.45	1.395	1.346
3 mg/kg	1.471	1.365	1.3
6 mg/kg	1.44	1.288	–
10 mg/kg	1.434	1.223	1.152

SUVr = standardized uptake value ratio.

Source: Data derived from presented slide at ADPD conference.

Figure 2 Individual Dose–Exposure Relationship Observed in the Aducanumab Phase Ib Trial (PRIME)



AUC = area under the concentration–time curve.

Note: Subjects demonstrating low cumulative aducumab exposures were primarily due to missed doses.

Source: Hang et al. 2015.

2.3 POPULATION PK-PD METHODS

2.3.1 Structural PK-PD Model

Several structural PK-PD models were evaluated to best describe the link between exposure and SUVr PET. The tested models included a direct relationship, as well as an indirect relationship, using an effect-compartment model to take into account a time delay for the concentrations in serum to reach the effect site.

Furthermore, several types of drug effect were tested, including a linear model, a power model, an E_{max} model, and a sigmoid E_{max} model.

No placebo models were evaluated because no specific placebo response was noticed during the observations period.

An additive error model was used for the residual variability. The baseline PET SUVr values were used as covariate in the model, but with an associated residual error of the same magnitude of the additive error model.

Inter-individual variability was tested on the PK-PD parameters by assuming a log-normal distribution.

2.3.2 PK-PD Model Selection and Evaluation

Models were selected by means of visual inspection of basic goodness-of-fits plots, including, but not limited to, plots of the observed data versus population (PRED) and individual predictions (IPRED), plots of individual weighted residuals (IWRES) versus IPRED, and the distribution of weighted residuals (WRES) over time. Relative standard errors (RSE) of the parameters were also compared to measure parameter precision. The NONMEM objective function value (OFV) was used to discriminate between nested models. This discrimination was based on a significance level of 0.05, which corresponds to a decrease of >3.84 in OFV (for one degree of freedom), as the difference in OFV is approximately χ^2 distributed.

Additionally, visual predictive check (VPC) was performed to test the model appropriateness by means of computing confidence intervals (CIs) derived from 1000 simulated data sets, using the final model and final parameter estimates, for each statistic (i.e., the median, the 5th and the 95th percentiles). Several VPCs were performed, either to test the appropriateness of the model when predicting the gantenerumab and aducanumab pooled dataset or to focus separately on the two compounds datasets. Furthermore, they were produced per level of exposure as well as per level of doses.

2.3.3 Computer Programs

The analyses were performed in NONMEM Version 7.2, using FOCE INTERACTION (Beal and Sheiner 1992). Graphics and NONMEM datasets were created using Version 3.1.2 and/or the SAS system for Windows, Version 9.3.

2.4 COVARIATE ANALYSIS

Only limited covariate information was available from the aducanumab data, and an exploratory graphical analysis of individual post-hoc parameters was conducted only for the following covariates: PET baseline values, compound type, sex, and dose.

3. RESULTS

3.1 DATA

The final PK-PD dataset combining aducanumab and gantenerumab data included 237 patients with a total of 693 PET SUVr observations.

3.2 POPULATION EXPOSURE SUVr PET MODEL

The relationship between exposure and the PET SUVr reduction time course was best described by using a power model combined with an effect compartment to account for the delay between exposure and PET response. The model equations are as follows:

$$\mathrm{PET(time)} = \mathrm{Base} * \left(1 - \mathrm{SLOP} * (\mathrm{Conc_E(time)})^{\mathrm{POW}}\right)$$

with $$\frac{\mathrm{dConc_E(time)}}{\mathrm{dtime}} = \mathrm{Ke0} * (\mathrm{Conc(time)} - \mathrm{Conc_E(time)})$$

with Base the individual PET SUVr baseline value, $\mathrm{Conc_E}$ the predicted concentration at effect site, Conc the predicted concentration in serum, $\mathrm{Ke0}$ the rate constant for drug transfer from serum to effect compartment, and SLOP and POW the parameters driving the drug effect.

Parameter values are reported in Table 3.

Table 3 Estimated Population PK-PD Parameters

Parameter	Mean (RSE%)	Value Inter-Individual Variability (RSE%)
Ke0 (Day $^{-1}$)	1.74×10^{-3} (38%)	127.3% (14%)
Equilibration half-life (weeks)	57	
SLOP	0.019 (33%)	—
POW (–)	0.716 (11%)	—
ADD_ERR	0.0659 (5%)	

ADD_ERR = additional error; KeO = rate constant for drug transfer from serum to the effect compartment; PD = pharmacodynamic; PK = pharmacokinetic; POW = power; RSE = relative standard error; SLOP = slope.

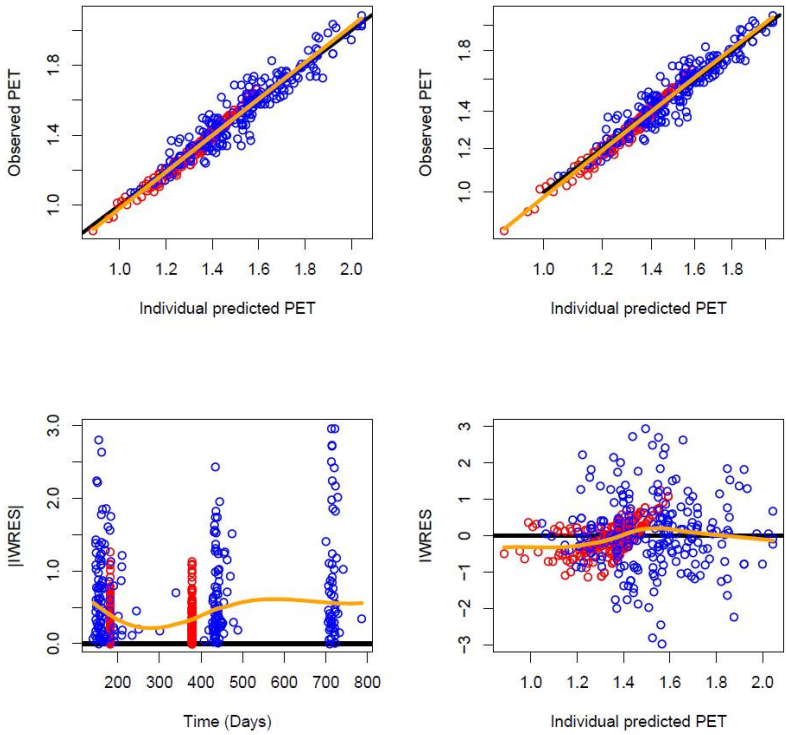
Inspection of the goodness-of-fit plots reported in Figure 3 shows that the final PK-PD model describes the data adequately without obvious bias in the population or individual predicted PET values. The VPCs are shown in Figures 5–7. The shaded areas indicate the 90% CIs (i.e., 5th and 95th percentiles) computed from simulations. The median and

the 5th and 95th percentiles of the observed PK profiles are contained in their respective CIs, indicating that the final PK-PD model captures both the central tendency and the between-subject variability of both gantenerumab and aducanumab pharmacodynamics in the target populations of patients with prodromal and mild Alzheimer's disease.

3.3 COVARIATE ANALYSIS

The exploratory graphical covariate analysis is reported on Figure 4. Although a small trend between PET baseline values and estimated individual Ke0, this graphical analysis did not reveal any relevant covariate relationships that would require further investigation.

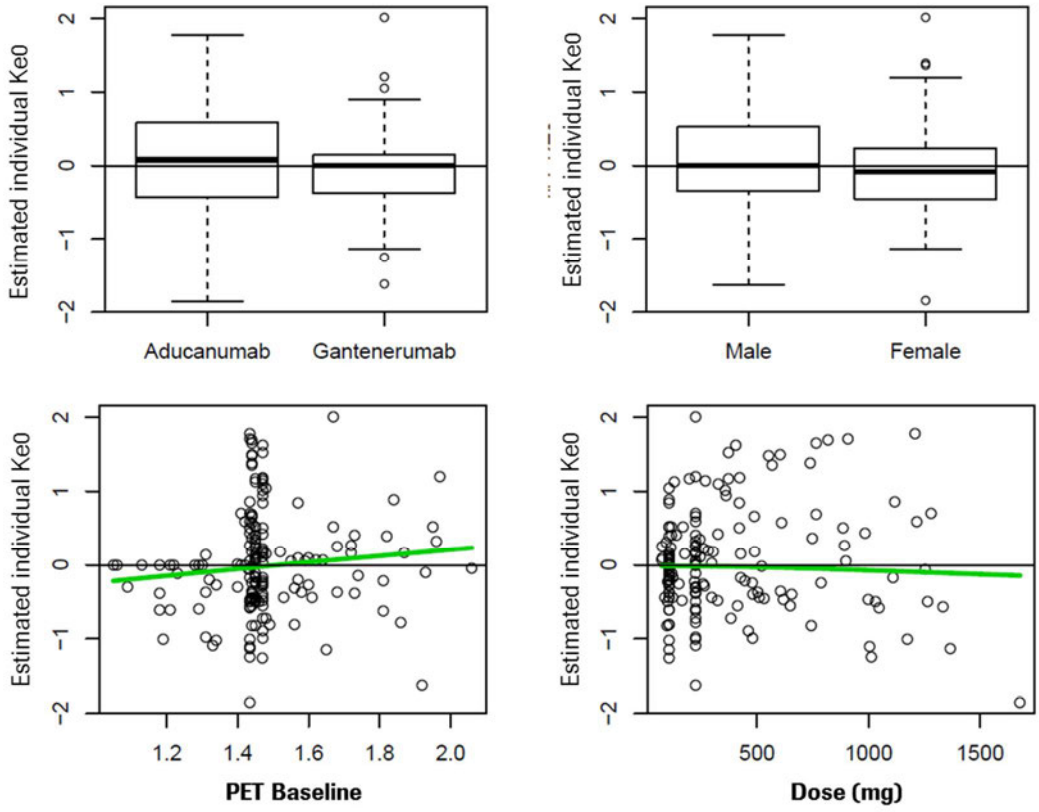
Figure 3 Goodness-of-Fit Plots for the Final PK-PD Model



IWES = individual weighted residual value; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

Note: The red dots represent the aducanumab compound, and blue dots represent gantenerumab compound. The orange lines correspond to a smoothing of the data.

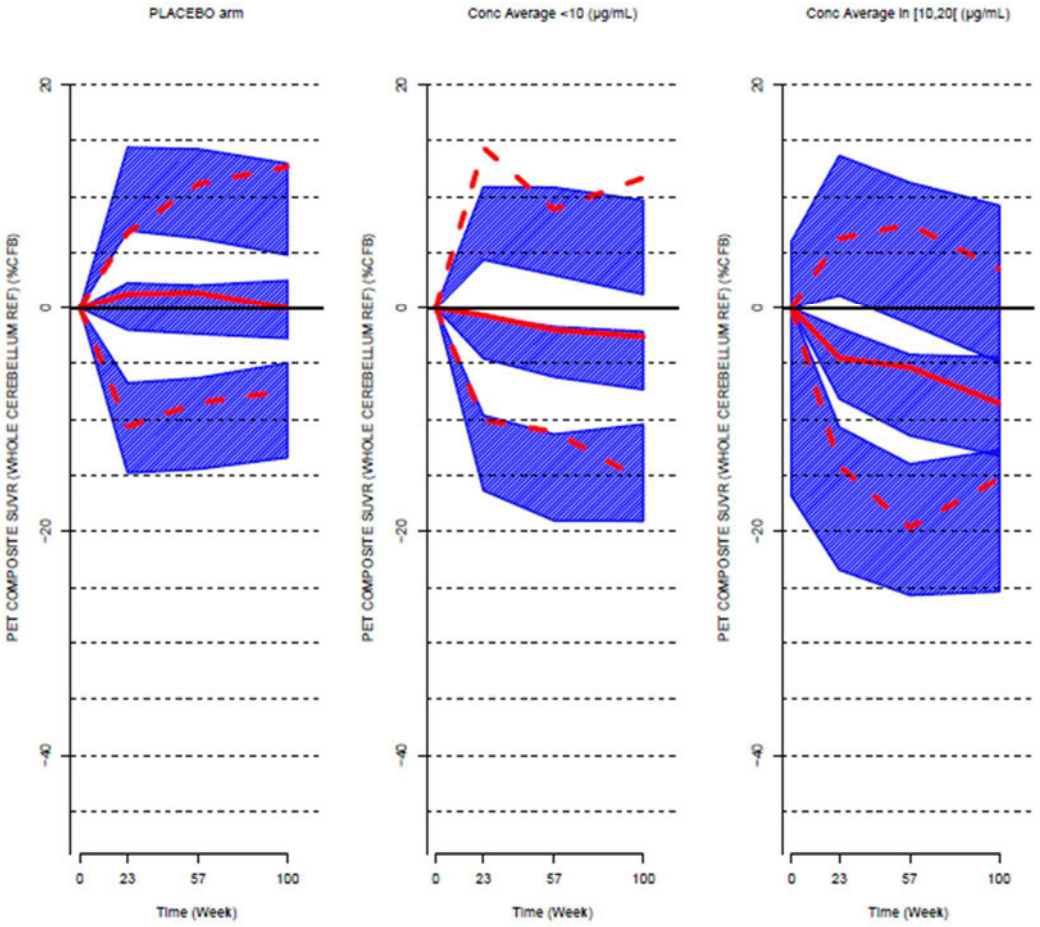
Figure 4 Exploratory Analysis of Covariates (by Compound Type, Sex, PET Baseline Value, and Dose [in milligrams] Value with Respect to Estimated Individual Ke0)



KeO = rate constant for drug transfer from serum to the effect compartment; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

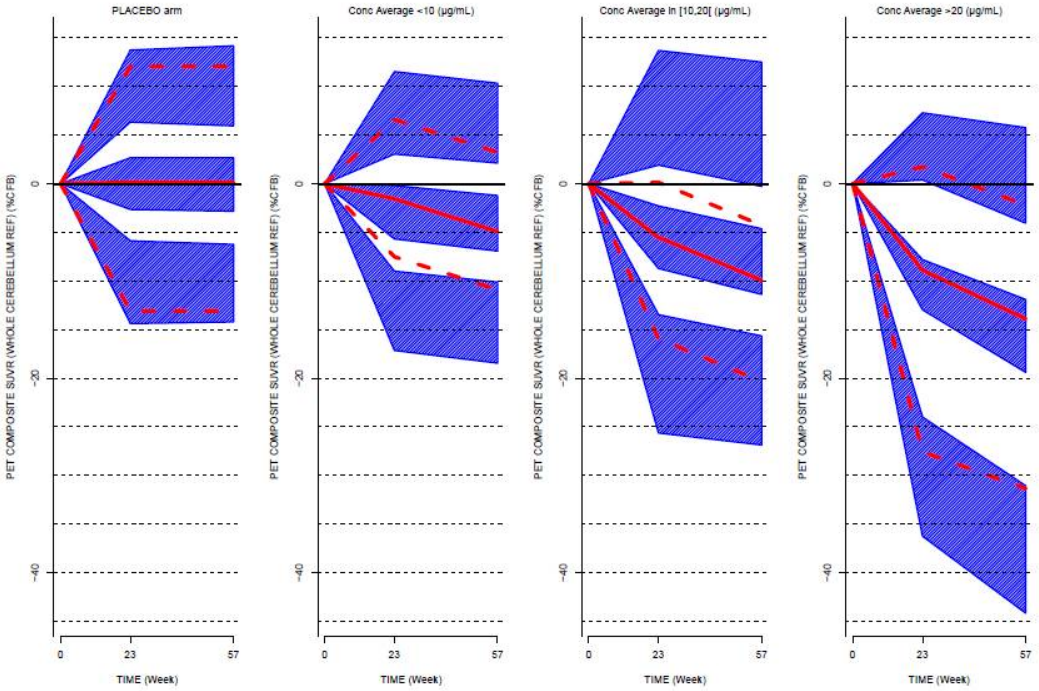
Note: Dose was investigated in milligrams, using a mean weight of 70 kg for doses the aducanumab PRIME study. The green line corresponds to a smoothing of the data.

Figure 5 Visual Predictive Check of the PET Model by Category of Serum Concentration Exposure for the Gantenerumab WN25203 Alone



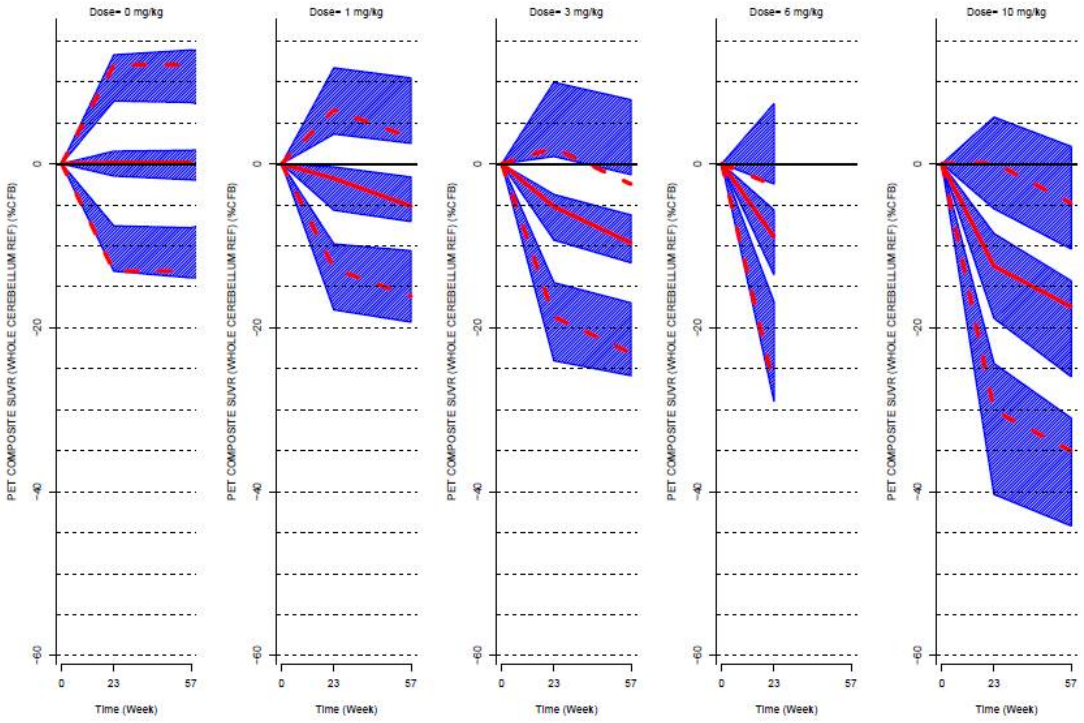
CFB = change from baseline; Conc = concentration; KeO = rate constant for drug transfer from serum to the effect compartment; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

Figure 6 Visual Predictive Check of the PET Model Per Category of Serum Concentration Exposure for the Aducanumab PRIME Study Alone



KeO = rate constant for drug transfer from serum to the effect compartment; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

Figure 7 Visual Predictive Check of the PET Model by Category of Expected Dose Group for the Aducanumab PRIME Trial Alone



KeO = rate constant for drug transfer from serum to the effect compartment; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

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Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model

1. BACKGROUND

Hutmacher et al. (2013) presented a pharmacodynamic (PD) model for bapineuzumab addressing the first occurrence of amyloid-related imaging abnormalities, or ARIAs, of "vasogenic edema" (ARIA-E) events. Patients received constant dose regimens of 0.5, 1, and 2 mg/kg given every 13 weeks over 1.5 years. A total of 2435 patients with 243 ARIA-E events were analysed. As shown below, a log hazard model was developed that included three elements:

- A baseline value (I_{BS}) reflecting a constant ARIA-E hazard for apolipoprotein E allele ε4 (*APOE* ε4) gene carriers and non-carriers, respectively
- Plasma drug concentrations (c) of bapineuzumab modulating the ARIA-E hazard through the maximum effect (E_{max}) of drug and 50% of the effective concentration (EC_{50}) parameters
- A time component continuously suppressing the ARIA-E hazard by the time (t) since first dosing. ET_{50} and γ modulated this effect.

$$\log h(t) = I_{BS} + \frac{E_{\max} \cdot c(t)}{c(t) + EC_{50}} \cdot \frac{ET_{50}^{\gamma}}{ET_{50}^{\gamma} + t^{\gamma}}$$

Because no model parameters were reported in Hutmacher et al. 2013, the parameters were derived from predicted time-concentration and time-hazard curves presented in Hutmacher et al. 2013 after digitizing the respective graphs for 0.5 mg/kg in *APOE ε4* carriers. I_{BS} parameters were obtained from the graphs directly, whereas the other parameters were calculated from the digitized data using MATLAB (or matrix laboratory) and maximum likelihood estimation. Parameter values are shown in Table 1.

Table 1 Estimated Pharmacodynamic Parameters for Bapineuzumab

I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (μg/mL)
8.7E-6 (non-carrier) 3.55E-5 (carrier)	323.441	2.146	6.891	2.64

2. ARIA EVENTS UNDER CONSTANT DOSING REGIMENS

The above model was applied to the double-blind phase of Study WN25203, in which patients received constant dose regimens of 105 and 225 mg of gantenerumab. Owing to paucity of ARIA event data and the assumed independence between time and study drug–related hazard model parameters, I_{BS}, ET_{50}, and γ were fixed to the bapineuzumab values, and only E_{max} and EC_{50} were estimated.

The concentration-time course for gantenerumab in Study WN25203 was derived from a population PK model previously developed for Phase I studies. It covers both intravenous (IV) and subcutaneous (SC) administration, as well as single and multiple repeated doses every 4 weeks, with a range of dose values for the repeated dose administrations from 6 mg to 200 mg for IV administration, 105 mg and 225 mg for SC administration, and up to 300 mg SC and 400 mg for IV administration when given only once. The parameters for this model are presented in Table 2.

Table 2 Pharmacokinetic Parameters for Gantenerumab

CL (L/day)	Q (L/day)	V_2 (L)	V_3 (L)	k_a (1/d)	F1 (1/d)	D (1/d)
0.336	0.869	3.152	6.38	0.22	0.494	0.0821

An update of the population PK model parameters was not considered as newly available drug concentrations were within prediction ranges from the established PK model. The maximum likelihood estimation of the log hazard model parameters E_{max} and EC_{50} was performed using NONMEM software. ARIA-E events were interval censored with a cutoff at 742 days. A total of 797 patients with 50 ARIA-E events were analysed.

Parameter estimates are shown in Table 3.

Table 3 ARIA-E Parameters for Gantenerumab

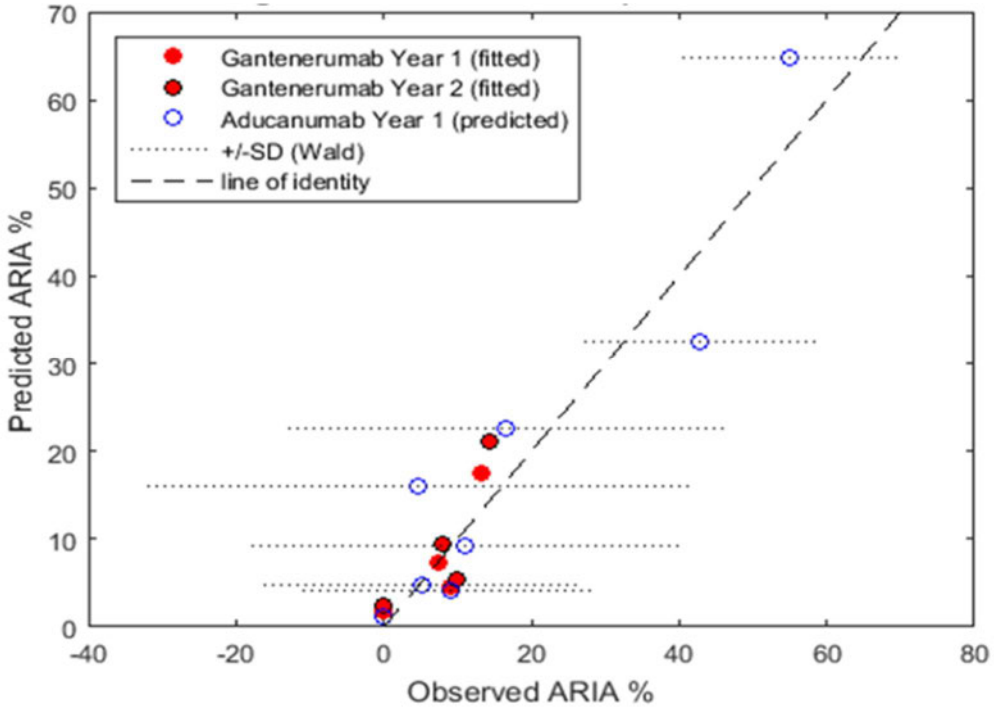
I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (μg/mL)
8.7E-6 (non-carrier) F 3.55E-5 (carrier) F	323.44 F	2.15 F	6.05±2.33	8.60±7.13

amyloid-related imaging abnormality–edema/effusion; F = fixed.

On inspection of the aducanumab PRIME study data (Sevigny et al. 2015), it became clear that the PK properties of gantenerumab and aducanumab are very similar. This supported an opportunity to test the hazard PK-PD model applied to gantenerumab on IV aducanumab ARIA-E data. The ARIA–E model, which already provides a good description of the gantenerumab ARIA-E data in Study WN25203 after 1 and 2 years of treatment, respectively, also predicted the aducanumab Phase Ib ARIA-E data with a great degree of accuracy (see Figure 1), including the ARIA rate differences across *APOE* ε4 allele groups (see Figure 2), even though this approach is limited based on external aggregated data. This finding indicated that doses much larger than those

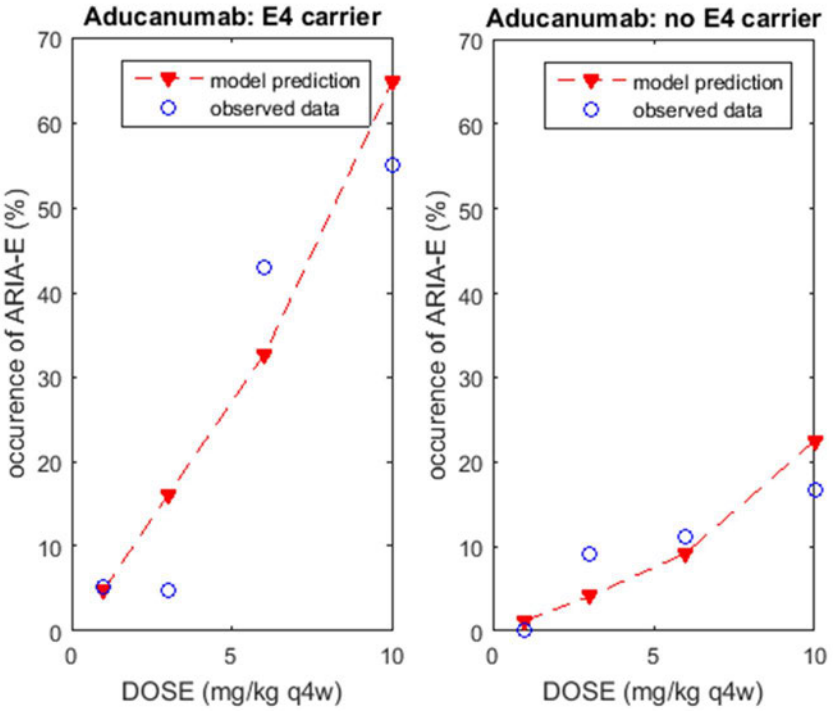
given in Study WN25203 can be described by the hazard model, provided that a constant dose regimen is used.

Figure 1 ARIA-E Prediction for IV Aducanumab Using Bapineuzumab Hazard Model Adapted to SC Gantenerumab



ARIA = amyloid-related imaging abnormality; ARIA-E = amyloid-related imaging abnormality–edema/effusion; IV = intravenous; SC = subcutaneous; SD = standard deviation.

Figure 2 Model-Based Predictions of ARIA-E Occurrence for Aducanumab by *APOE ε4* Carrier and Non-Carrier Status and Dose for a Q4W Dosing Regimen: Comparison to Observed Data in the PRIME Study



APOE ε4= apolipoprotein E, allele ε4; ARIA = amyloid-related imaging abnormality; ARIA-E = amyloid-related imaging abnormality–edema/effusion; IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous.

3. ARIA EVENTS UNDER DOSE TITRATION REGIMENS

3.1 MODELING DATABASE AS OF 6 DECEMBER 2016

To check the validity of the model under titration conditions, two patient groups were selected from the open-label extension studies of WN25203 and WN28745. The first group comprised 71 patients who received increasing doses of gantenerumab and received placebo during the double-blind phase of the study. The second group comprised 417 patients who received a constant dose of gantenerumab and who did not have treatment-free intervals of more than 70 days. The first group is representative for the intended Phase III design, and the second group was included to enhance the database and link the model to previously established results (see Table 4).

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Table 4 Patient Population Included in ARIA-E Model Building (Database as of 6 December 2016)

Number of Patients (Number of Events)	Study WN25203	Study WN28745	Total	Comment
Total included in study	**797 (63)**	**371 (35)**	**1168 (108)**	
Placebo treatment	236 (2)	111 (3)	347 (5)	Excluded from model building
Total included in study on active drug	**561 (61)**	**260 (32)**	**821 (103)**	
Total on active drug before OLE, or treatment gaps >70 days	125 (11)	108 (23)	333 (44)	Excluded from model building
Total included in model building	**436 (50)**	**52 (9)**	**488 (59)**	
Titrated without prior treatment	19 (1)	52 (9)	71 (10)	Included in model building
Constant dosing, and treatment gaps <70 days	417 (49)	—	417 (49)	Included in model building

ARIA-E = amyloid-related imaging abnormality–edema/effusion; OLE = open-label extension.

As noted previously, the maximum likelihood estimation was performed using NONMEM software. Estimated model parameters were E_{max} , EC_{50} and the baseline risk for carriers and non-carriers. ARIA-E events were observation interval censored.

Parameter estimates are shown in Table 5.

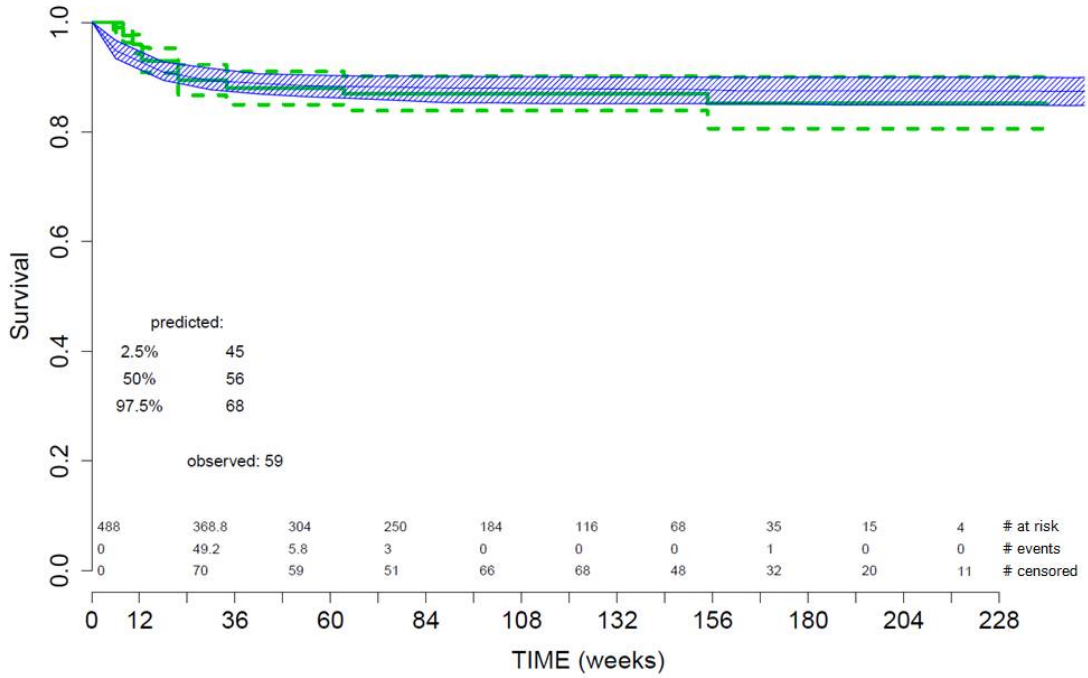
Table 5 ARIA-E Parameters for Gantenerumab When Applied to Titration Data

I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (μg/mL)
5.84 ± 4.22 E-6 (non-carrier) 11.9 ± 7.30 E-6 (carrier)	323.44 F	2.15 F	7.12 ± 1.03	5.16 ± 2.85

ARIA-E = amyloid-related imaging abnormality–edema/effusion; F = fixed.

Visual predictive checks were performed to assess model performance. As shown in Figure 3, the overall model performance was acceptable. Figure 4 presents a condition that was excluded from the model building. The apparent bias in the prediction might be attributable to a SCarlet RoAD study effect, which will be followed up during ongoing completion of the database.

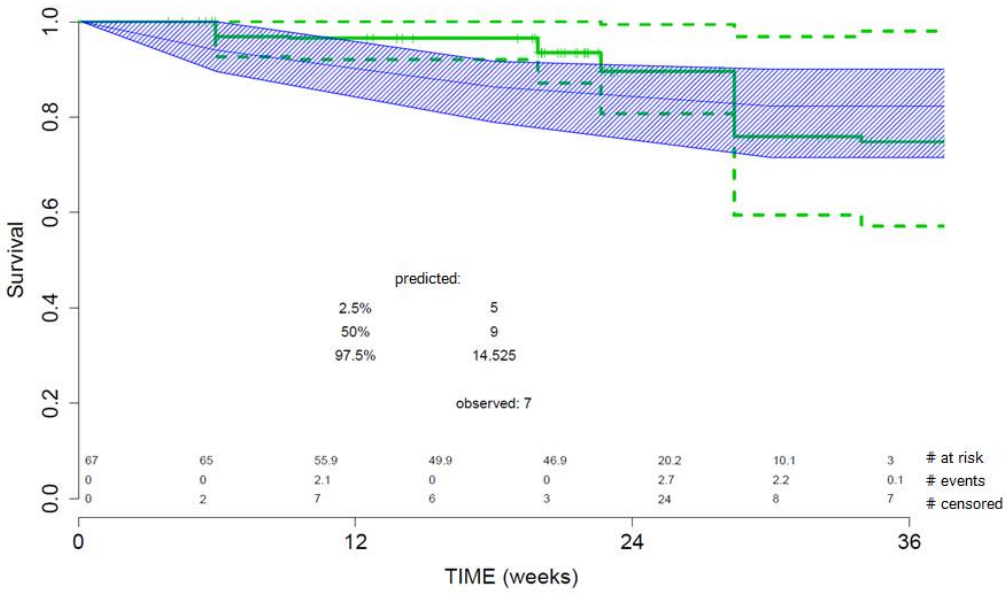
Figure 3 Visual Predictive Check on Database Used for Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% [median], and 97.5%) and the actual observed number of events.

Figure 4 Visual Predictive Checks: Patients in SCarlet RoAD Study with Treatment Interruption >70 Days from Time 0 at Start of Open-Label Extension WN25203



ARIA-E = amyloid-related imaging abnormality–edema/effusion; OLE = open-label extension.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% [median], and 97.5%) and the actual observed number of events.

3.2 MODELING DATABASE AS OF 3 MARCH 2017

Table 6 presents an updated ARIA-E model building using data based on the cutoff date of 3 March 2017. In Table 7, ARIA-E parameters for gantenerumab are summarized when applied to titration data.

Table 6 Patient Population Included in ARIA-E Model Building (Database as of 3 March 2017)

Number of Patients (Number of Events)	Study WN25203	Study WN28745	Total	Comment
Total included in study	**797 (69)**	**371 (60)**	**1168 (129)**	
Placebo treatment	234 (2)	108 (3)	342 (5)	Excluded from model building
Database cleaning ongoing	3 (0)	—	3 (0)	Excluded from model building
Total included in study on active drug	**560 (67)**	**263 (57)**	**823 (124)**	
Long-term constant dose before titration	64 (9)	83 (17)	147 (26)	Excluded from model building
Total included into model building	**496 (58)**	**180 (40)**	**676 (98)**	
Titrated without prior treatment	24 (2)	67 [18]	91 (20)	Included in model building
Doses always smaller or equal to 225 mg	472 (56)	113 (22)	585 (78)	Included in model building

ARIA-E = amyloid-related imaging abnormality–edema/effusion.

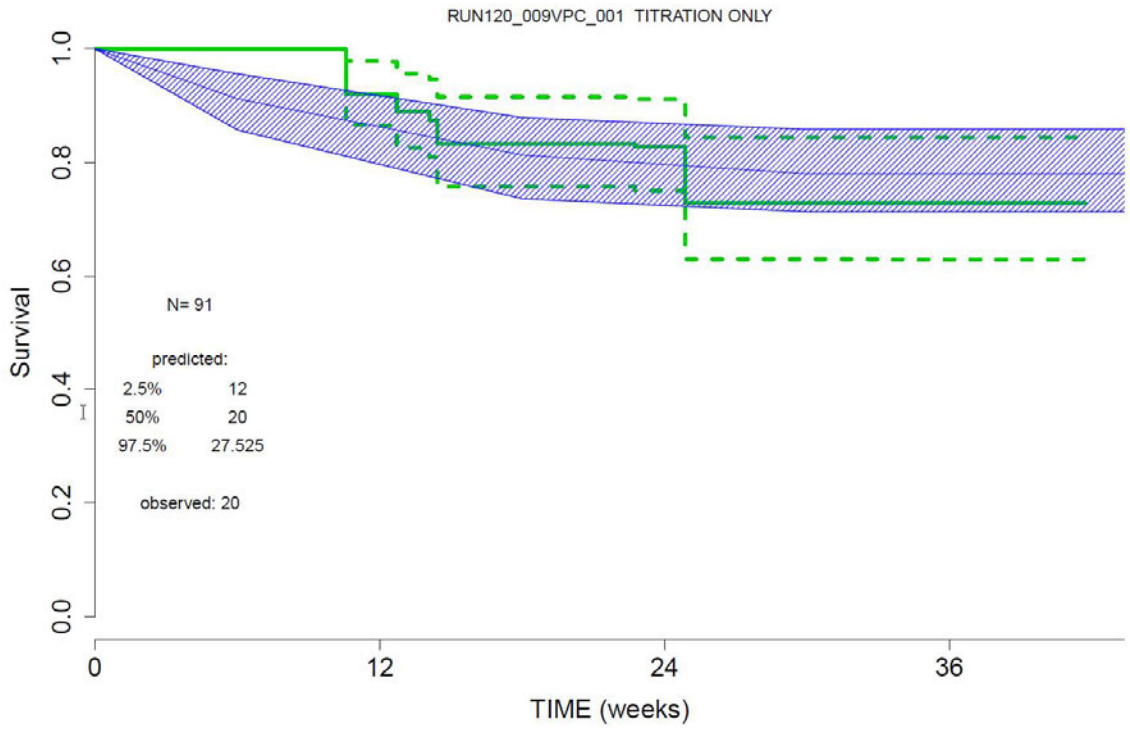
Table 7 ARIA-E Parameters for Gantenerumab when Applied to Titration Data

I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (µg/mL)
2.36 ± 1.01 E-5 (non-carrier) 3.75 ± 1.30 E-5 (carrier)	323.44 F	2.15 F	6.07 ± 0.702	7.75 ± 2.70

ARIA-E = amyloid-related imaging abnormality–edema/effusion; F = fixed.

Figures 5–7 show visual predictive checks for the final model. For both patients groups selected for model building, the diagnostics look acceptable (see Figures 5 and 6). For the excluded patient group who exhibited constant gantenerumab dosing followed by titration, often with 1 to 2 years of treatment gap in between, the diagnostics indicate a considerable mismatch. This could not be corrected by introducing covariates (such maximum treatment gap) into the model. It appears that the hazard model with its time component is not flexible enough for such regimens.

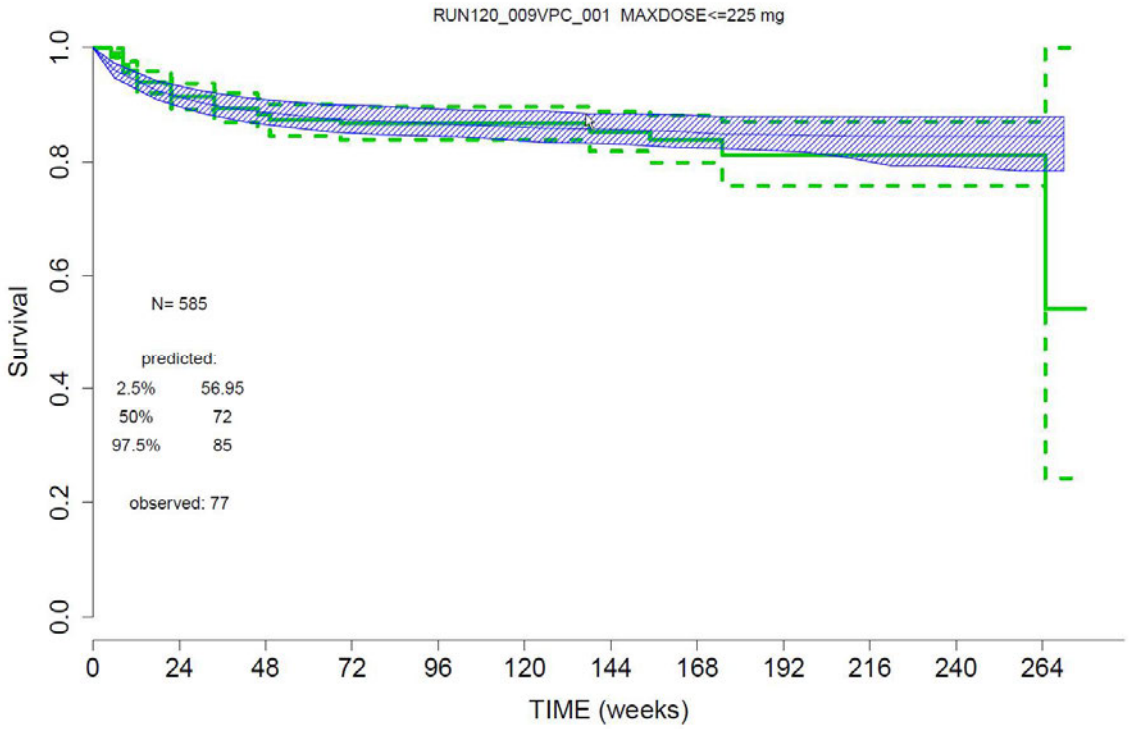
Figure 5 Visual Predictive Check on Titration Data Used for Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events (2.5%, 50% [median], and 97.5% percentiles), and the actual observed number of events. The apparent mismatch over the first 12 weeks is because no scan was performed during this period. Survival refers to the ARIA-E event-free proportion.

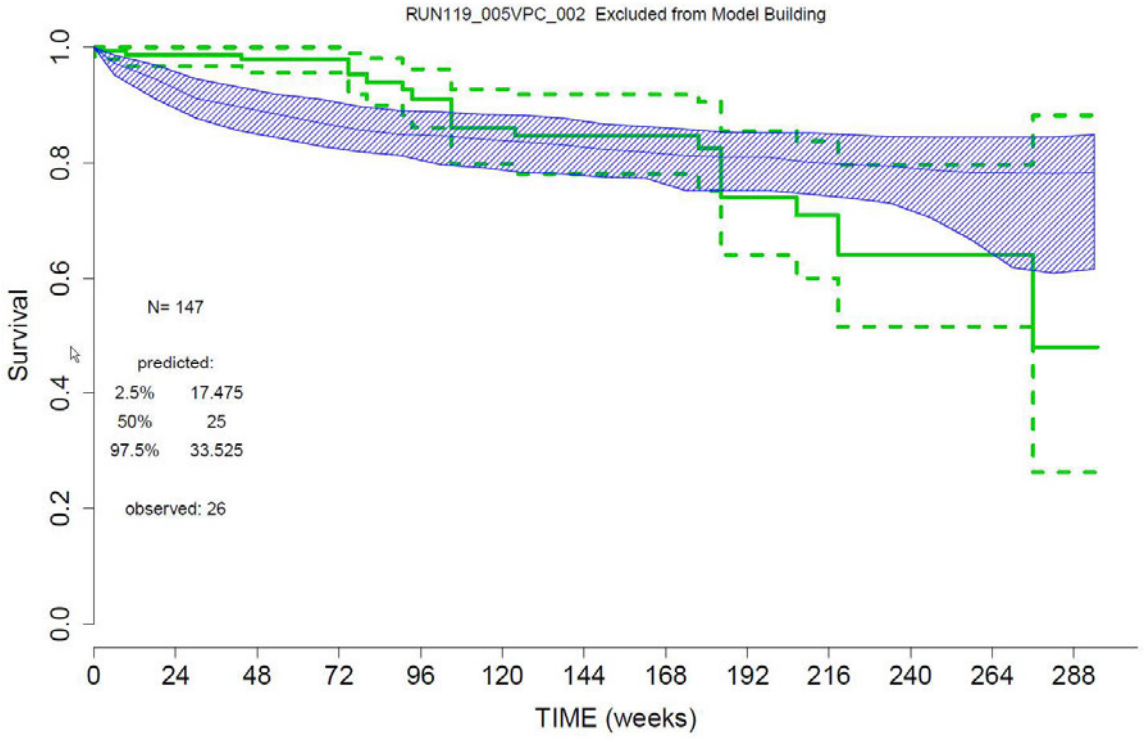
Figure 6 Visual Predictive Check on Data Used for Model Building (Based on Data from Patients Enrolled in the Double-Blind WN25203 and WN28745 Studies and Dosed with 225 mg)



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% (median), and 97.5%) and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

Figure 7 Visual Predictive Check on Excluded Data from Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% (median), and 97.5%) and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

3.3. MODELING DATABASE AS OF 8 JULY 2017

Table 8 presents an updated ARIA-E model building using data based on the cutoff date of 8 July 2017. In Table 9, ARIA-E parameters for gantenerumab are summarized when applied to titration data.

Table 8 Patient Population Included in ARIA-E Model Building (Database as of 7 July 2017)

Number of Patients (Number of Events)	Study WN25203	Study WN28745	Total	Comment
Total included in study	797 (75)	371 (60)	1168 (135)	
Placebo treatment	227 (2)	108 (3)	335 (5)	Excluded from model building
Database cleaning ongoing	2 (0)	—	2 (0)	Excluded from model building
Total included in study on active drug	568 (73)	263 (57)	831 (130)	
Long-term constant dose before titration	66 (14)	80 (16)	146 (30)	Excluded from model building
Total included into model building	502 (59)	183 (41)	685 (100)	
Titrated without prior treatment	36 (3)	70 (19)	106 (22)	Included in model building
Doses always smaller or equal to 225 mg	466 (56)	113 (22)	579 (78)	Included in model building

ARIA-E = amyloid-related imaging abnormality–edema/effusion.

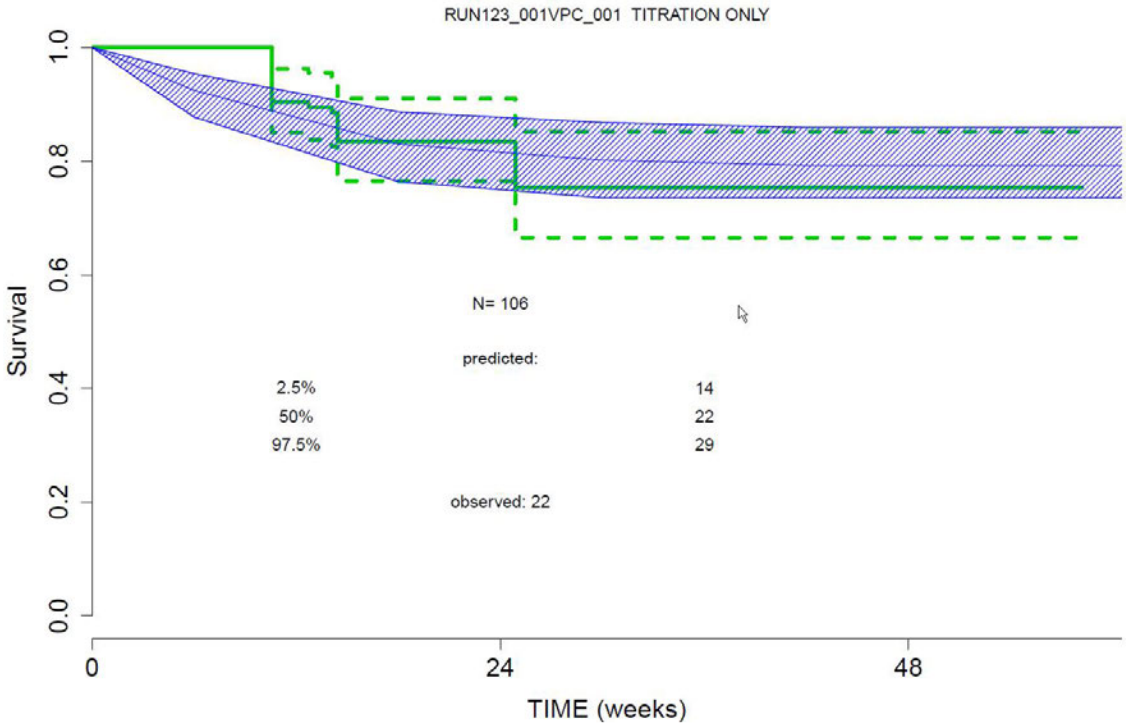
Table 9 ARIA-E Parameters for Gantenerumab when Applied to Titration Data

I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (μg/mL)
2.14 ± 0.9742 E-5 (non-carrier) 3.52 ± 1.24 E-5 (carrier)	323.44 F	2.15 F	5.92 ± 0.688	6.78 ± 2.88

ARIA-E = amyloid-related imaging abnormality–edema/effusion; F = fixed.

Figures 8–10 show visual predictive checks for the final model. For both patients groups selected for model building, the diagnostics look acceptable (see Figures 8 and 9). For the excluded patient group who exhibited constant gantenerumab dosing followed by titration, often with 1 to 2 years of treatment gap in between, the diagnostics indicate a considerable mismatch. This could not be corrected by introducing covariates (such maximum treatment gap) into the model. It appears that the hazard model with its time component is not flexible enough for such regimens.

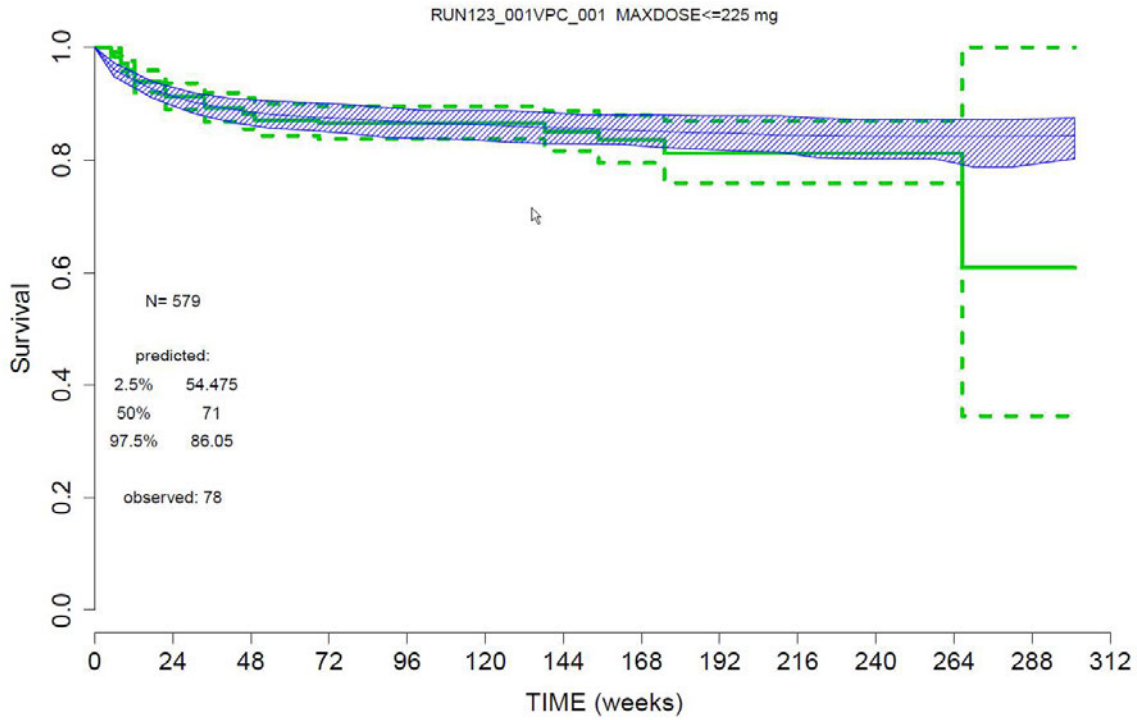
Figure 8 Visual Predictive Check on Titration Data Used for Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events (2.5%, 50% [median], and 97.5% percentiles), and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

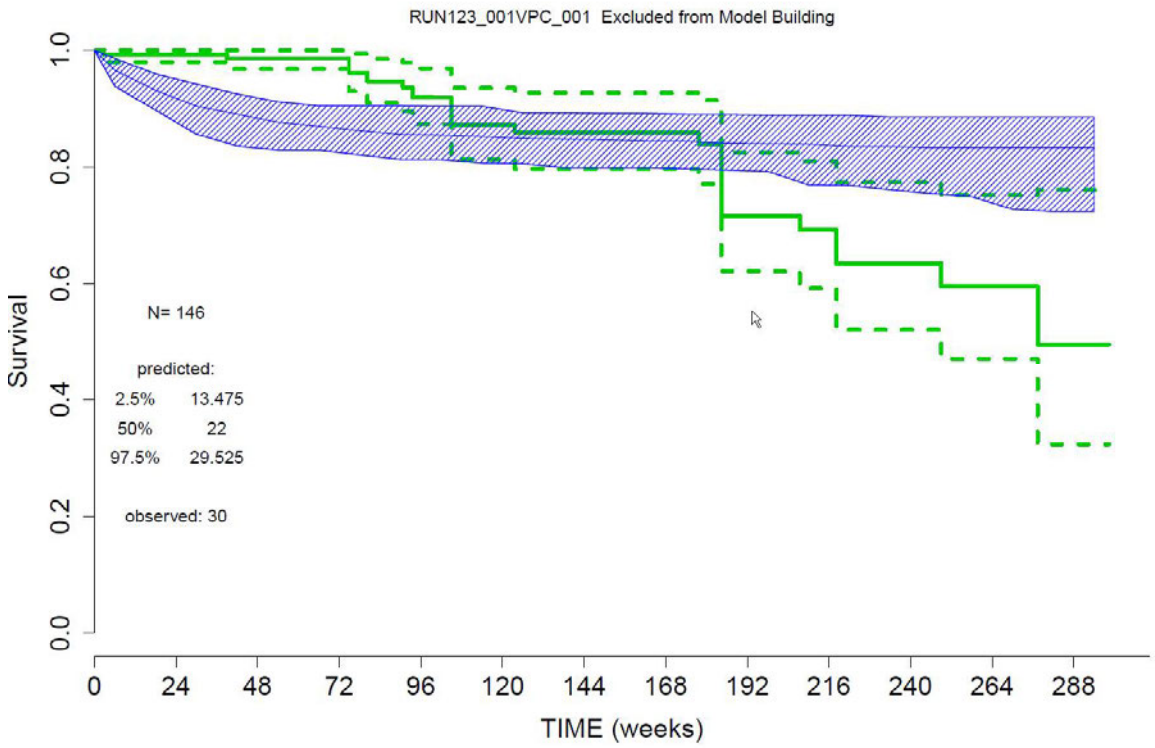
Figure 9 Visual Predictive Check on Data Used for Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% (median), and 97.5%) and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

Figure 10 Visual Predictive Check on Excluded Data from Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% (median), and 97.5%) and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

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Sevigny J, Chiao P, Williams L, et al. Randomized, double-blind, Phase 1b study of BIIB037 in patients with prodromal or mild Alzheimer's disease. 12th International Congress on Alzheimer's and Parkinson's Disease. Symposium 26 March 2015. Nice, France.

Appendix 6
Management Rules for Amyloid-Related Imaging Abnormalities

Event	Characteristics	Action to Be Taken
ARIA-E	Asymptomatic ARIA-E and BGTS <4	• Continue study drug at the same dose level (i.e., do not uptitrate) and repeat MRI scan 4 weeks later. – As long as BGTS is <4 and ≥1, continue study drug at the same dose level and repeat MRI 4 weeks later. – Once ARIA resolves, resume uptitration and obtain an MRI scan per the titration schedule. For participants randomized to the Q2W regimen, perform another MRI scan 3 months after $ARIA\ resolution$.
	Symptomatic ARIA-E (of any size) or asymptomatic ARIA-E and BGTS ≥4	• Temporarily interrupt study drug and perform MRI scans at 4-week intervals until symptoms and ARIA-E resolve. • When symptoms and ARIA-E resolve, reintroduce study drug at dose given at the time the event was detected. – Perform an MRI scan before next scheduled dose for participants randomized to the Q4W regimen or after the second dose for participant randomized to the Q2W regimen. – If no new ARIA-E is detected, resume uptitration and obtain an MRI per titration schedule. For participants randomized to the Q2W regimen, perform another MRI scan 3 months after study drug reintroduction.
	Any recurrence of ARIA-E	• Treat the same as the first event (based on symptoms and BGTS).
ARIA-H	>15 ARIA-H cumulatively (should not include any disseminated LH)	• Discontinue study drug.

Appendix 6: Management Rules for Amyloid-Related Imaging Abnormalities (cont.)

ARIA-E = amyloid-related imaging abnormality–edema/effusion; ARIA-H=amyloid-related imaging abnormality–hemosiderin deposition; BGTS=Barkhof grand total score; LH=leptomeningeal hemosiderosis; MRI=magnetic resonance imaging;Q2W=every 2 weeks.

In exceptional cases of (1) an ARIA-E that is asymptomatic with BGTS <4 and considered stable over consecutive MRI images by the Sponsor and investigator; or (2) symptomatic ARIA-E for which the imaging evidence of ARIA-E has resolved but the CNS symptoms continue, study drug can be either reintroduced or uptitrated, as applicable, and 4-weekly MRI monitoring may no longer be necessary, as determined by the Sponsor and investigator.

Symptomatic ARIA-E is defined as onset or worsening of CNS symptom(s) that is/are temporally associated with ARIA-E MRI findings

A PK and a plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria

GRADUATE II (PROTOCOL WN39658)

SUMMARY OF CHANGES

A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY, AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE

PROTOCOL AMENDMENT, VERSION 2: RATIONALE

Protocol WN39658 has been amended to present the results of the relative bioavailability study (WP40052) and to adjust the dosing regimen of Study WN39658 according to these results. In addition, the entry criteria of the study population have been reviewed to increase the homogeneity of the study population and to better target the right population (early Alzheimer's).

The changes below, along with a rationale for each, have been updated as follows:

- Data from the World Health Organization on Alzheimer's disease has been updated (Section 1.1).
- Safety and efficacy data from open-label extension (OLE) WN25203 and WN28745 studies have been updated. Figure 4 (OLE Results 6–9 Months at High Dose) has been added; subsequent figures have been renumbered accordingly (Sections 1.2.2, 1.2.2.3, 1.2.2.4, 1.2.3, 1.3.1, 1.3.2, 1.3.5).
- Language in the clinical studies section has been updated to reflect recent information from the relative bioavailability study (WP40052) (Section 1.2.2.5).
- The dosing regimen has been adjusted to reflect the results of the relative bioavailability study WP40052 (Sections 1.3.2, 1.3.3, 1.3.5, 3.3.1, 3.3.3, 3.3.4, 4.3.1.1, and 4.3.2.1, and Table 1, Figure 6, and Appendix 1).
- The key secondary designation has been removed; consequently the hierarchization of the secondary endpoints has also been removed. Section 3.3.7 has been deleted; subsequent sections have been renumbered accordingly (Sections 2 and 6.4.2).
- The Coding (also called Digit Symbol Substitution Test) has been added to the secondary endpoints to have a broader range of cognitive domains assessed (Sections 2, 4.5.5.1, 4.5.5.6, 4.6.2, 4.6.5, 4.6.6, and Appendix 1). Section 4.5.5.6 has been added and subsequent sections have been renumbered accordingly.
- Language has been updated to reflect changes in the study design, including China extension enrollment and analyses (Sections 3.1.1, 3.2, 3.3.1, 4.1, 4.2, 6, 6.1, and 6.8).
- For operational reasons, the Mini-Mental State Examination has been added to the optional prescreening, and the screening period has been extended by 4 weeks (Sections 3.1.1, 3.2, and 4.6.1 and Appendix 1).
- Inclusion and exclusion criteria have been updated to clarify the criteria and to further improve the safety and data quality (Sections 4.1.1, 4.1.2.1, 4.1.2.3, 4.1.2.6, and 4.1.2.7).
- With respect to blinding, the roles of the study personnel have been refined to clarify and improve the blinding (Sections 4.3.2.1 and 4.5.5.1).
- Wording around the regulatory status of the amyloid positron emission tomography (PET) tracers has been added (Section 4.3.2.2) and the PET tracer safety reporting process has been clarified (Sections 5.3.1 and 5.4.2.1).

- It has been clarified that benzodiazepine used to treat a mood or anxiety disorder as maintenance treatment is not permitted medication (Section 4.4.1).
- Cognitive, functional, and health economics assessments have been clarified to include descriptive categories, recall periods, and total score ranges as appropriate (Sections 4.5.5.1, 4.5.5.8, 4.5.5.9, 4.5.5.10, and 4.5.5.13).
- A biomarker serum sample has been added at screening and subsequent visits to allow additional analyses (Section 4.5.6.2 and Appendix 1).
- Patient non-compliance rules have been adapted to be applicable to every 4-week and every 2-week dosing regimens (Section 4.7.2).
- Reporting requirements for medical device complaints have been included (Sections 5.3 and 5.4.4).
- Reporting of serious adverse events and adverse events of special interest has been modified to be until the patient's last visit (including long-term follow-up visits) (Section 5.3.1 and 5.4.2.2). As a result, Section 5.6 "Adverse Events That Occur after the Adverse Event Reporting Period" has been deleted and subsequent sections have been renumbered.
- It has been clarified that sites are not expected to review the clinical outcome assessment data for adverse events (Section 5.3.5.14).
- Language has been changed for clarity and consistency regarding reporting of injection-site reactions (Section 5.3.5.2).
- Medical monitor information has been updated to reflect a change in the Medical Monitor (Section 5.4.1).
- The determination of sample size and an increase in sample size have been clarified (Section 6.1).
- The ARIA model has been updated (Section 3.3 and Appendix 5; Table 8, Table 9, and Figures 8–10 have been added to Appendix 5).
- To summarize the list of the prohibited medications, a table has been added as Appendix 7.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 3:

RATIONALE

Protocol WN39658 has been amended to clarify the sample size of this study. While protocol wording allowed an increase of up to 1140 patients based on factors external to the study, the Sponsor wanted to clarify that upon initial learnings from external studies, a decision was made to increase the power of the study. Thus, the sample size has been increased from 760 participants per study to 1016 (508 patients randomized to gantenerumab and 508 randomized to placebo). This is described in detail in Section 6.1. In addition, Protocol WN39658 has been amended to allow the first patients enrolled in the study to enroll in an open-label extension (OLE) as planned. Details on this procedure and the OLE schedule of activities have been added.

Changes to the protocol, along with a rationale for each change, are summarized below:

- Language in the clinical studies section has been updated to reflect the most recent safety and efficacy information from the OLE WN25203 and WN28745 studies (Sections 1.2.2.3, 1.2.2.4, 1.2.3, 1.3.1)
- The objectives and endpoints section has been updated to include the objectives and endpoints for the OLE period of the study (Section 2)
- Details on the OLE procedures, such as eligibility, assessments, study duration, and follow-up have been added (Sections 3.1.1, 3.2, 3.3.4.2, 3.3.5, 4.1.1, 4.1.3, 4.2, 4.3.2.2, 4.6.4, 4.6.6, 4.6.7, 4.7.1, Appendix 1)
- Further details on the China Enrollment Plan have been provided (Sections 3.1.1, 4.1, 6.8)
- The China Food and Drug Administration (CFDA) is now called the National Medical Products Administration (NMPA), and the terms in the protocol have been updated accordingly (Sections 3.1.1, 4.1, 6)
- Additional substudy details, including details related to the optional interim analyses, have been provided (Sections 3.1.2, 6.4.3, 6.7.2)
- Sample size-related information has been updated as described above (Sections 4.1, 6, 6.1)
- Time windows for certain study visits and procedures have been clarified (Sections 4.3.2.1, 4.3.2.2, 4.5.5, 4.6.1, 4.6.3, 4.6.4, 5.1.2, Appendix 1)
- Language has been added to clarify that GV-971 is not a permitted medication in this study (Sections 4.1.1, 4.1.2.7, 4.4.1)
- Language has been added to clarify that body weight should be obtained each time creatinine clearance is tested and that genitourinary system examination is optional (Section 4.5.3, Appendix 1)
- Language has been added to clarify that a plasma sample should be collected along with the pharmacokinetic sample each time the site becomes aware of the occurrence or worsening of ARIA-E or the occurrence of ARIA-H meeting discontinuation criteria (Sections 4.5.6.2, 5.1.2, Appendix 1)
- Wording in the immunogenicity section has been clarified (Section 5.1.1.3)
- Management of patients who experience select adverse events has been clarified (Sections 5.1.2, 5.3.5.1, Appendix 6)
- Language related to injection reactions (Section 5.3.5.2) and abortions (Section 5.4.3.2) has been updated

- Emergency medical contact information has been updated (Section 5.4.1)
- The procedures for reporting adverse events that occur after the adverse event reporting period (Section 5.6) and for expedited adverse event reporting have been clarified (Section 5.7)
- Exploratory efficacy analyses have been added (Section 6.4.3)
- Appendix 7 has been removed

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 4:

RATIONALE

Protocol WN39658 has been amended in response to the COVID-19 pandemic due to the SARS-CoV-2 virus. Restrictions imposed globally during the COVID-19 pandemic are expected to affect protocol-specified activities, including administration of study drug, and could decrease the power of the study. This amendment extends the double-blind treatment period by 12 weeks in order to mitigate the impact of missed administrations and to preserve the scientific integrity of the study by enabling more participants to receive study drug at the initially intended exposures. The continuing impact of the COVID-19 pandemic on study procedures will be closely monitored, and if there are greater than anticipated disruptions to study drug administration, the amendment also allows the option of further extending the double-blind treatment period by another 12 weeks. These extension periods are described in Section 3.3.4.1. For the same reason, the upper limit of the sample size has been increased from 1140 to 1322 (Section 6.1).

Please note that the extension of treatment by 12 or 24 weeks is not expected to adversely impact the risks/benefits that were previously described for this study.

Changes to the protocol, along with a rationale for each change, are summarized below:

- In the Objectives and Endpoints section (Section 2), wording has been changed from "Week 104" to "Week 116" to accommodate the study extension of 12 weeks or to "Week 128" to accommodate the study extension of 24 weeks (12 weeks plus an additional 12 weeks if applicable) (Table 2).
- The description of the study was clarified to include a description of 2 scenarios due to COVID-19 related disruptions. In scenario 1, participants who are active in the double-blind treatment period after implementation of Protocol Version 4 will have the double-blind treatment period extended by 12 weeks, up to Week 116. In scenario 2, participants who are active in the double-blind treatment period after implementation of Protocol Version 4 will have the double-blind treatment period extended by an additional 12 weeks, up to Week 128 (Section 3.1.1). Participants who have completed the double-blind treatment period prior to implementation of Protocol Version 4 will continue into the OLE or safety follow-up periods following Week 104 assessments, as per the original schedule.
- The descriptions of the length of the double-blind treatment period and the total study length were updated to reflect the study extension(s) of 12 weeks or 24 weeks (12 weeks plus an additional 12 weeks if applicable) of the double-blind treatment period (Section 3.2).
- Appendix 1 was updated to incorporate the double-blind treatment period extension(s).
- For CSF-enrolled patients, the optional CSF collection timepoint was shifted from Week 52 to Week 76 (Appendix 1) in order for CSF to be collected between screening and the final efficacy and safety visit of the double-blind treatment part of the study.
- The number and/or timing of dosing visits, assessments, study completion visits, and follow-up assessments was updated to reflect the two possible double-blind treatment period extensions (Sections 4.3.2.1, 4.6.3, 4.6.6, 4.6.7).
- Use of approved monoclonal antibodies (except to prevent or postpone cognitive decline) has been removed from the Exclusion Criteria (Section 4.1.2) and Prohibited Medications (Section 4.4.2) because their use has become more common within the study population. These drugs do not raise any safety concerns if used in the study and are not expected to have drug-drug interactions with gantenerumab.

- The timing of the primary efficacy outcome measure was updated to accommodate the study extension(s) of 12 weeks or 24 weeks (12 weeks plus an additional 12 weeks if applicable) (Section 6.4.1).
- The timing of the planned interim analysis was changed from 24 months to 116 weeks (or to 128 weeks, if the study is extended by an additional 12 weeks) after 50% of the targeted study enrollment has been reached (Section 6.7.1).
- The protocol now states that every effort will be made to minimize missing data and to expedite the implementation of Protocol Version 4 (Section 6.4.1).
- In case a participant's study partner changes, collection of data using the Zarit Caregiver Interview–Alzheimer's Disease (ZCI) scale will continue (rather than stop) in order to minimize missing data (Section 4.5.5.9).
- The volume of the blood sample collected for plasma biomarker assessment was increased by 6 mL to ensure that the volume is sufficient for analyses (Section 4.5.6.2).
- Wording was added to indicate that unused PK sample material may also be used for the assessment of exploratory plasma biomarkers in order to align with the ICF (Section 4.5.6.4).
- "Patient" has been replaced with "participant" as appropriate throughout to be consistent with current best practices for studies of Alzheimer's disease.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

The changes to the protocol, along with a rationale for each change, are summarized below:

- Section 1.3.5 Overall Benefit-Risk Summary has been updated to address the COVID-19 pandemic impact on the Benefit-Risk assessment for Study WN39658, as per the MHRA requirement
- Objectives and endpoints of the Double-Blind Treatment Period (Table 2) have been updated in the following manner:

  - Corresponding endpoints for the 'exploratory efficacy' objective have been revised to remove 'in global outcome' as a criteria for the measurement of change from baseline to Week 116, which was added in error.

  - The exploratory endpoint 'Time to clinically evident decline, defined as an increase of ≥2.0 in CDR-SOB subscore or 1 in at least four items of the FAQ' has been removed from Table 2, as it is not considered relevant anymore based on new available data.

  - The exploratory endpoint 'Change from baseline to Week 116 measured by 'Function as assessed by the CDR function subscore" has been removed as it is no longer considered relevant based on new available data.

  - The exploratory endpoint 'clinically evident decline as measured using the CDR' has been added to Table 2.

  - The pharmacokinetic (PK) objective of the study has been changed to an exploratory PK objective to be consistent with the sparse PK sampling design and population modeling used to analyse the dose concentration–time data of gantenerumab. In addition, the protocol has been amended to enable early access PK, anti-drug antibodies (ADA) and pharmacodynamic (PD) biomarker samples. Early access will only be applied if there are sufficient sample data available to make an adequate assessment.

  - The corresponding endpoints for the pharmacodynamic (PD) biomarker objective have been revised to clarify the duration of change as a measurement from baseline to Week 116 when assessing brain amyloid load, brain tau load and cerebral spinal fluid markers.

  - The PD biomarker objective endpoint 'MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all participants ' has been reclassified as exploratory as it is no longer considered secondary based on new available data.
- Sections 3.1.1 and 4.1.3 have been updated to clarify that the open-label extension (OLE) of Study WN39658 is not applicable in countries that cannot run Study WN42171.
- Sections 4.1.2.7, 4.4.1, 4.7.2, and Appendix 1 have been revised to clarify the Medical Monitor's responsibility to review and support patient cohort management and other protocol activities. Any reference to approval by the Medical Monitor with regards to medical decisions following enrollment has been removed from the protocol. The Principal Investigator (PI) may consult with the Medical Monitor/Sponsor for advice or clarification and may share risk factor information pertinent to the patient, but the medical decisions for the study participants are the responsibility of the PI.
- Section 4.1.3 has been amended to replace Week 104 with Week 116 (or Week 128, if applicable) which was omitted in the previous protocol amendment.

- Section 4.6.3 and 4.6.4 have been amended to better clarify the order of assessments during the study visits.
- Section 6.4.1 has been updated according to the estimand framework outlined in the ICH-E9 draft addendum with regards to the primary endpoint.
- Section 6.4.2 has been updated to remove the reference to time to event, which was included in error.
- Sections 6.4.4, 6.5 and 6.6 have been updated to clarify that a separate cut off may be necessary for PD biomarker, PK, and ADA samples to allow early access to PD biomarker samples and ensure expedient data analyses. Section 6.7.1 and 6.7.2 have been updated to include additional details surrounding the conduct of an interim analysis, should one be implemented.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

STATISTICAL ANALYSIS PLAN

STUDY TITLE: **TWO PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP EFFICACY AND SAFETY STUDIES OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**

STUDY NUMBER: WN29922, WN39658

STUDY NAME: GRADUATE I, GRADUATE II

VERSION NUMBER: 1.0

ROCHE COMPOUND(S): Gantenerumab (RO4909832)

EUDRACT NUMBER: 2017-001364-38 (WN29922)
2017-001365-24 (WN39658)

IND NUMBER: 102,266

NCT NUMBER: NCT03444870

PLAN PREPARED BY: [redacted], [redacted]

STATISTICAL ANALYSIS PLAN APPROVAL

Date and Time(UTC)	Reason for Signing	Name
12-Oct-2021 07:30:26	Company Signatory	[redacted]

SPONSOR: F. Hoffmann-La Roche Ltd
LEGAL REGISTERED ADDRESS: Grenzacherstrasse 124
4070 Basel, Switzerland

DATE FINAL: See electronic date stamp above

STATISTICAL ANALYSIS PLAN VERSION HISTORY

This SAP was developed based on Roche SAP model document v2.0, revised 26 October 2020.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	see electronic date stamp on title page	Version 5.0, 21 September 2021

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
Aβ	amyloid-beta
AD	Alzheimer's disease
ADA	anti-drug antibody
ADAS-Cog11 / Cog13	Alzheimer disease assessment scale – cognition, subscale 11 / 13
ADCS-ADL	Alzheimer disease cooperative study - activities of daily living
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
APOE	apolipoprotein ε
ARIA-E	amyloid-related imaging abnormalities – edema/effusion
ARIA-H	amyloid-related imaging abnormalities – hemosiderin deposition
CDR-GS	clinical dementia rating – global score
CDR-SOB	clinical dementia rating – sum of boxes
CIR	copy increments from reference
CNS	central nervous system
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
CSR	Clinical Study Report
C-SSRS	Columbia-suicide severity rating scale
DTI	diffusion tensor imaging
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EQ-5D	EuroQol-Five Dimensions
FAQ	functional activities questionnaire
FDA	(U.S.) Food and Drug Administration
ICE	intercurrent event
ICH	International Council on Harmonization
iDMC	independent Data Monitoring Committee
IRC	independent review charter
ISR	injection-site reaction
ITT	intent to treat
IxRS	interactive voice/web-based response system
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat

MMRM	mixed effects model repeated measures
MMSE	mini-mental state examination
MNAR	Missing not at random
MRI	magnetic resonance imaging
NMPA	National Medical Products Administration
NPI-Q	neuropsychiatric inventory-questionnaire
NSDCR	not study drug or condition related
OLE	open-label extension
PET	Positron emission tomography
PK	pharmacokinetic
pTau	phosphorylated tau
Q2W	every 2 weeks
Q4W	every 4 weeks
QoL	quality of life
QoL-AD	quality of life – Alzheimer's disease
RUD-Lite	resource utilization in dementia - lite
SAE	serious adverse events
SAP	Statistical Analysis Plan
SC	subcutaneous
SDCR	study drug or condition related
SUV	standard uptake value
SUVR	standard uptake value ratio
tTau	total tau
ZCI-AD	Zarit caregiver interview – Alzheimer's disease

1. INTRODUCTION

This document describes the statistical analyses that will be reported in the Clinical Study Reports (CSR) of studies WN29922 and WN39658. All the description and analyses presented in this document apply to each study separately. This document will focus on the statistical methodology underlying the report. The efficacy estimands and safety endpoints that will be the basis for comparing treatments will be defined in full in this document along with the populations of participants that are to be used in the analyses.

This Statistical Analysis Plan (SAP) covers analyses planned for the double-blind treatment period in the studies only. Analyses planned for tau-PET substudies are provided in Section 5.7.5.1. Analyses planned for the longitudinal amyloid PET are described in a separate document, the amyloid PET substudy SAP. The pharmacokinetic (PK) data will be reported in the population PK report and therefore not covered in this document. Similarly health economic data (such as utility values derived from EQ-5D) will be analyzed and reported separately from the clinical study report and are therefore not covered here.

The description of layouts for the CSR outputs, the details about the underlying analysis datasets and programs, and the linking of production outputs to sections in the CSR are not within the scope of this document and will be covered in separate documents, i.e., Data Analysis Plan Module 2 and 3.

The language used in this SAP supersedes that in the protocol and protocol synopsis.

An early draft of this SAP was presented to U.S. Food and Drug Administration (FDA) in the context of a Type C meeting (Written Response Only procedure, December 21, 2020, Ref ID: 4720726) and to the European Medicines Agency (EMA) in the context of scientific advice procedure (EMA Written Advice received on 29 January 2020). These procedures focused on the proposed primary estimand, the estimator and other aspects of the analysis plan. Both agencies in principle agreed on the primary question of interest in the context of the estimand framework (ICH E9[R1]). There was also agreement on the proposed hierarchy of secondary endpoints. The feedback received during these health authority interactions was duly considered and informed the current version of this SAP.

1.1 OBJECTIVES

The primary trial objective is to demonstrate superiority of gantenerumab (hereafter referred to as ‘active drug’) over placebo, 116 weeks after initiating treatment in an early (prodromal to mild) Alzheimer’s disease (AD) population.

Table 1 Objectives and Corresponding Endpoints

Primary Objective(s)	Corresponding Endpoint(s)
● To evaluate the efficacy of gantenerumab administered by SC injection compared with placebo	● The change in global outcome from baseline (Day 1) to Week 116, as measured by the CDR-SOB
Secondary Objective(s)	**Corresponding Endpoints**
● To evaluate the efficacy of gantenerumab versus placebo on cognition and/or function	The change from baseline to Week 116 in cognition and/or function, as measured by: ● MMSE total score ● ADAS-Cog11 and ADAS-Cog13 ● Verbal Fluency Task ● Coding ● FAQ ● ADCS-ADL total score and instrumental score
Exploratory Objective(s)	**Corresponding Endpoints**
● To evaluate the efficacy of gantenerumab versus placebo	The change from baseline to Week 116 in the following: ● Clinically evident decline as measured using the CDR ● Severity, as assessed by the CDR Global Score ● Dependence level, as derived from the ADCS-ADL score ● Health-related quality of life, as assessed by the QoL-AD scale ● Behavioral and neuropsychiatric symptoms of AD, as measured by the NPI-Q ● Study partner burden, as assessed by the ZCI-AD scale ● Elements of resource utilization, as assessed by the RUD-Lite ● Health outcomes in participant and study partner, as measured by EQ-5D questionnaire

Safety Objective(s)	Corresponding Endpoints
● To evaluate the safety of gantenerumab compared with placebo	● Nature, frequency, severity, and timing of adverse events and serious adverse events ● Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and C-SSRS ● Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H ● Nature, frequency, severity, and timing of injection-site reactions ● Presence of ADAs during the study relative to the presence of ADAs at baseline (in active drug group only)
Pharmacodynamic Biomarker Objective	**Corresponding Endpoints**
● To evaluate the effect of gantenerumab compared with placebo	● Change from baseline to Week 116 in brain tau load, as measured by tau PET scan in a subset of participants ● Change from baseline to Week 116 in cerebrospinal fluid markers of disease in a subset of participants, including, but not limited to total tau, and phosphorylated tau
Exploratory Biomarker Objective	**Corresponding Endpoints**
● To evaluate the effect of gantenerumab compared with placebo	● Change over time in plasma and other CSF biomarkers ● Change from baseline to Week 116 in functional brain connectivity, as measured by resting-state functional MRI (where available) ● Change from baseline to Week 116 in integrity of white matter, as measured by DTI-MRI (where available) ● Change in MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all participants

AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale-Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale-Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group-Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities-edema/effusion; ARIA-H = amyloid-related imaging abnormalities-hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating-Sum of Boxes; CSF = cerebrospinal fluid; C-SSRS = Columbia-Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory-Questionnaire; PET = positron emission tomography; QoL-AD = Quality of Life-Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia-Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview-Alzheimer's Disease.

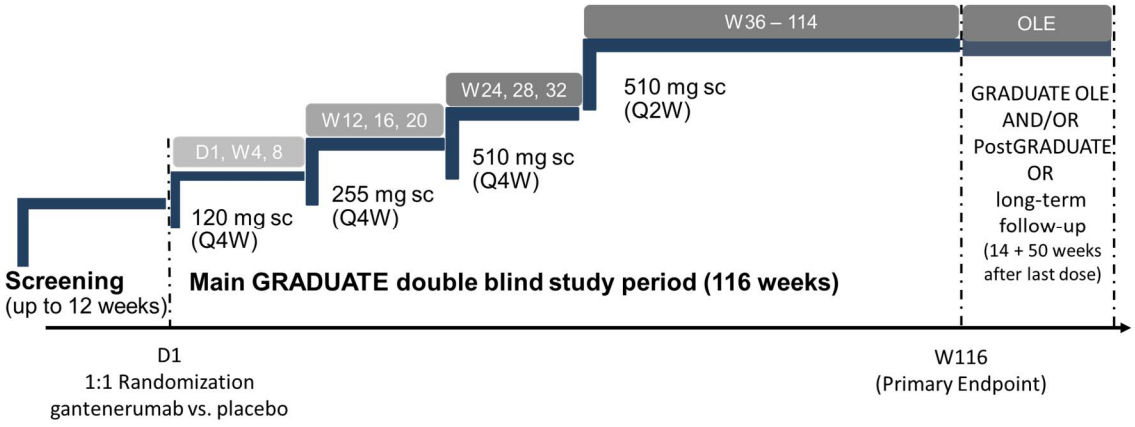
1.2 STUDY DESIGN

These are two identical Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies designed to evaluate the efficacy and safety of gantenerumab in participants with early (prodromal to mild) AD.

The planned number of participants for the global enrollment phase for each study is approximately 1016 participants randomized in a 1:1 ratio to receive active drug or placebo (508 participants randomized to active drug and 508 randomized to placebo) (see Section 3). To maintain a balanced number of participants enrolled in each treatment arm and to ensure that the arms are comparable, randomization will be stratified by stage of the disease (prodromal AD vs. mild AD), apolipoprotein E (APOE) allele status (presence vs. absence of the ε4 allele), use of AD medication (presence vs. absence), geographic region (Western Europe and Australia vs. Rest of the World vs. North America) and participation in the longitudinal amyloid and tau PET substudies. Approximately 175 centers in approximately 15 countries worldwide will participate in these studies.

Due to the global impact of the coronavirus disease (COVID-19) pandemic and the resulting disruption in study drug administration, the duration of the double-blind treatment period was extended by 12 weeks, with Protocol Amendment 4. The optional scenario of a further extension of 12 weeks – resulting in a final efficacy and safety visit at Week 128 – was not implemented. An overview of the study design is provided in Figure 1.

Figure 1 Overall Study Design



Each study consists of three distinct periods:

Screening (including an optional prescreening): The screening period may last up to 12 weeks for each eligible participant.

Double-blind treatment period: After screening, participants who meet all eligibility criteria will be randomly assigned to one of two arms (active treatment or placebo) in a 1:1 ratio. Following baseline assessments, each participant will receive a minimum of 9 subcutaneous (SC) administrations every 4 weeks (Q4W) of study drug (uptitration period), followed by up to 40 administrations every 2 weeks (Q2W) of study drug at target dose in the double-blind treatment period. The last dose of study drug will be administered at Week 114. At the end of the double-blind treatment period, 2 weeks after the last dose, all participants will undergo the final efficacy and safety study visit. Participants who have already completed the double-blind treatment period prior to implementation of Protocol Version 4 will have received up to 34 SC Q2W administrations of study drug during the double-blind treatment period. The last dose will have been administered at Week 102, and their final efficacy and safety visit will be at Week 104.

The Sponsor will emphasize to investigators the importance of collecting data for the primary endpoint through Week 116, even if participants withdraw from treatment but do not withdraw from the study.

Post-double-blind treatment period: After the final efficacy and safety study visit for the double-blind treatment period, all participants will be asked to come back for the long-term follow-up visits or to continue in the open-label extension (OLE). Participants will either directly enter the separate WN42171 (PostGraduate) OLE study, or enter a parent study OLE period until they have completed uptitration (minimum 36 weeks) before rolling over to PostGraduate. This second option is for participants at sites where PostGraduate is not yet approved when they have reached the end of the double-blind treatment period.

China Enrollment Plan

Based on historical data, participant recruitment is expected to take longer in China; therefore, a specific China enrollment plan has been established. Thus, if at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the National Medical Products Administration (NMPA) during the global enrollment phase, additional participants may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. Only participants enrolled at NMPA-recognized sites, during the global enrollment phase, will be included in the primary analysis. All participants enrolled at NMPA-recognized sites, either during the global enrollment phase or the China extension phases, will be included in a China-specific analysis.

The China-specific analysis will be described in a separate SAP and therefore is not covered in this document.

1.2.1 Treatment Assignment and Blinding

Randomization will be performed centrally using an interactive voice or Web-based response system (IxRS). After screening, participants who meet all eligibility criteria will be randomly assigned to one of two treatment groups (active treatment or placebo). The ratio will be 1:1, one active to one placebo. The randomization method will be stratified block-randomization. Randomization to treatment allocation will be stratified by geographic region (Western Europe and Australia vs. Rest of the World vs. North America), participant APOE ε4 status (carrier vs. non-carrier), participant stage of disease (prodromal vs. mild AD), use of AD medication (presence vs. absence), and participation in the longitudinal amyloid and tau PET substudies. Except in circumstances in which a health authority, ethics committee, or institutional review board requires it, a participant will not be told of his or her APOE ε4 status. Individual participant APOE ε4 genotype results will be blinded to participants, investigators, and the Sponsor. APOE ε4 status information will be supplied directly to the IxRS vendor by the central testing laboratory so that the information can be incorporated at the time of randomization. For participants for whom APOE ε4 status is already known, the results will be blinded to the Sponsor and, as much as possible, to the site and central MRI reader.

The study is to be conducted in a double-blind manner to minimize potential bias from investigators and participants. The Sponsor will be blinded to study treatment. In the OLE period, the Sponsor, participants, and site staff will remain blinded to previous treatment allocation.

The randomization method implemented in the China extension cohort will be the same as that implemented in the global population.

1.2.2 Independent Review Facility

MRI scans will be reviewed by a central MRI core laboratory, which will perform the diagnostic reads and assessment of MRI outcome measures.

Central facilities will be used for PET assessments (see Independent Review Charter [IRC]).

1.2.3 Data Monitoring Committee

The iDMC will evaluate participant safety and efficacy on a regular basis. In addition to the data defined in the iDMC Charter (e.g., the incidence and nature of adverse events [AE], serious adverse events [SAE], adverse events of special interest [AESI], amyloid-related imaging abnormalities-edema/effusion [ARIA-E], amyloid-related imaging abnormalities-hemosiderin deposition [ARIA-H], and injection-site reactions [ISR]), the iDMC will review all necessary cumulative data at regular intervals during the study, including efficacy when needed. It is anticipated that these assessments will occur approximately every 3 months. At the time of each review, the iDMC will make

appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, the treatment regimen should be modified, the protocol should be amended, enrollment should be held pending further safety evaluations). The iDMC will also evaluate planned or unplanned interim analyses for efficacy or futility.

2. STATISTICAL HYPOTHESES

The primary efficacy analysis will compare the active drug arm to the placebo arm at Week 116 with a two-sided test corresponding to the following null hypothesis, H_0, and alternative hypothesis, H_1:

$$H_0: \mu_{active} = \mu_{placebo}$$

$$H_1: \mu_{active} \neq \mu_{placebo}$$

Where μ_{active} and $\mu_{placebo}$ are the mean change from baseline to Week 116 in the CDR-SOB score for each arm.

3. SAMPLE SIZE DETERMINATION

Determination of sample size is based on participants enrolled in the global enrollment phase. In each study, approximately 1016 participants will be enrolled and randomized in 1:1 ratio to each treatment arm (active drug or placebo) during the global enrollment phase. A sample size increase may be considered if factors external to the study or blinded study data review would warrant a change to the sample size assumptions.

Additional participants may be randomized during the China extension if at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA during the global enrollment phase.

The estimated sample size required to demonstrate efficacy with regard to CDR-SOB is based on the following assumptions:

- the mean change in the CDR-SOB from baseline to Week 104 is 2.5 points in the placebo arm
- a common standard deviation across treatment arms for change of approximately 2.97 from baseline to Week 104 in the CDR-SOB
- active drug has a true effect of a 30% relative reduction in deterioration of CDR-SOB

Based on these assumptions, and using a student's T-test with equal variance, a sample size was calculated for 90% power to detect a true treatment effect of 30% relative reduction in deterioration of CDR-SOB at a two-sided α of 0.05.

Uncertainties on parameters affecting the power (e.g., dropout rate, study drug discontinuation rate, standard deviation, and placebo decline) were assumed to be equivalent to a drop in sample size of up to around 35% and were corrected for accordingly. This calculation leads to a total of 1016 participants in the study.

At the date of writing Protocol Version 4, it is expected that participants would miss an average of 8 weeks of study drug administration over the course of the original 2-year study due to the COVID-19 pandemic. This had the potential to decrease the power of the study from ~90% to ~80%. To mitigate the impact of missed administrations, the double-blind treatment period has been extended by 12 weeks. Under current assumptions, this brings the study power back to the originally planned ~90%.

4. ANALYSIS SETS

The following populations are defined:

Table 2 Analysis Sets

Population	Definition	Scope
All enrolled participants	All participants enrolled during the global enrollment phase whether or not the participant received the assigned treatment. Analysis using this population will be performed by randomized treatment.	Patient disposition report will be based on this analysis set
Intent-to-treat (ITT)	All participants randomized during the global enrollment phase, who received at least one dose of study drug. Analysis using this population will be performed by randomized treatment.	All efficacy analyses, including the primary estimand, will be based on this analysis set.
CSF intent-to-treat (CSF-ITT)	All participants in the ITT population who had at least one post-baseline cerebrospinal fluid (CSF) measure of phosphorylated tau (pTau) or total tau (tTau). Analysis using this population will be performed by randomized treatment.	All analyses of CSF biomarkers will be based on this analysis set.
MRI intent-to-treat (MRI-ITT)	All participants in the ITT population who had at least one post-baseline volumetric MRI scan. Analysis using this population will be performed by randomized treatment.	All analyses of volumetric MRI parameters will be based on this analysis set.
Tau PET modified intent-to-treat (T-mITT)	All participants in the ITT population who have consented to the Tau PET substudy and had at least one post-baseline Tau PET scan. Analysis using this population will be performed by randomized treatment.	All analyses of Tau PET parameters will be based on this analysis set.
Safety-evaluable	All participants randomized during the global enrollment phase who received at least one dose of study drug. Any participant randomized to placebo who received at least one dose (any dose) of active treatment will be summarized as having received the active treatment. Analysis using this population will be performed by treatment actually received.	All safety analyses (with the exception of Safety MRI) will be based on this analysis set.
MRI Safety-evaluable	All participants in the Safety-evaluable population who had at least one post-baseline safety MRI scan. Analysis using this population will be performed by treatment actually received	All analyses of safety MRI will be based on this analysis set.

CSF-ITT = cerebrospinal fluid intent-to-treat; ITT = Intent-to-treat; MRI-ITT = MRI intent-to-treat; T-mITT = Tau PET modified intent-to-treat

5. STATISTICAL ANALYSES

5.1 GENERAL CONSIDERATIONS

In the following sections, for all continuous variables for which descriptive statistics are indicated, the following statistics will be reported: the number of observations, the mean, median, standard deviation, and minimum and maximum. The 25th and 75th percentiles

(Q1 and Q3) will also be reported for selected tables. Descriptive summaries of discrete data will include frequencies expressed in terms of number and percentage of participants.

For efficacy assessments, the baseline is defined as the assessment taken at the baseline visit (Day 1) up to and including the day of first study drug intake. If no assessment is reported at the baseline visit up to the day of first study drug intake, the earliest assessment reported after Day 1 and up to the day of second dose or Day 35, whichever is earlier, will be used as baseline. If no assessment is reported either at baseline visit or up to Day 35, an assessment reported at screening will be used as baseline. Day 35 is the latest timepoint allowed for Week 4 visit as per protocol.

For all other assessments, the baseline is defined as the last available assessment up to and including the day of first study drug intake, unless specified otherwise.

The efficacy analyses will be based on the ITT analysis set (see Table 2) and will compare the active drug arm against the placebo arm with regards to mean change from baseline to Week 116. Two-sided test hypotheses will be defined in the following sections and the type I error level will be 5%. There will be two identical Phase III studies, for each respective study the type I error level will be 5%. In order to protect the overall type I error rate (i.e., at each study level) when incorporating the hypothesis testing of multiple endpoints into the analysis, a fixed sequence testing procedure (Westfall and Krishen 2001) will be used to adjust for multiple comparisons. Testing of each hypothesis will follow a pre-specified order such that an endpoint would only be tested if the preceding one in the hierarchy was significant at 5% alpha level. The endpoint hierarchy, starting with the primary endpoint and including only confirmatory secondary endpoints, is the following:

1. CDR-SOB (Clinical Dementia Rating, Sum of Boxes)
2. ADAS-Cog 13 (Alzheimer's Disease Assessment Scale, Cognitive subscale, 13-item)
3. ADCS-ADL (Alzheimer's Disease Cooperative Study, Activities of Daily Living scale) total score
4. FAQ (Functional Activities Questionnaire)

Missing outcome data will be handled using data imputation aligned with the targeted estimand, see Section 5.3.3 for a detailed description of the analysis strategy.

When using a statistical model with baseline covariate adjustment, missing baseline covariate data other than the baseline outcome measure will be imputed to the overall median value for continuous covariates, or will be imputed to the most frequent category for categorical variables.

In statistical model using change from baseline of a given outcome measure as the dependent variable, participants with missing baseline outcome measure will be excluded from the analysis. There will be no imputation of baseline value for clinical outcome measures.

The impact of the COVID-19 pandemic on the study and its conduct will be monitored and the overall impact will be assessed and described in the Clinical Study Reports.

5.2 PARTICIPANT DISPOSITION

The analysis of participant disposition will be based on all randomized participants (see Analysis sets in Table 2). The number of participants randomized will be tabulated by country, site, and treatment arm. Participant disposition (the number of participants randomized, treated, and completing through the primary endpoint timing, as well as the end of study) will be tabulated by treatment arm. Premature study drug discontinuation and study discontinuation, as well as reasons for discontinuations, will be summarized.

Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm. Separate tables will be provided for COVID-19-related major protocol deviations and reasons for COVID-19-related major protocol deviations.

5.3 ENDPOINT ANALYSIS

5.3.1 Definition of Primary Endpoint

As detailed in the study protocols, the primary endpoint is the Clinical Dementia Rating Sum of Boxes (CDR-SOB) which is a global scale covering both functional and cognitive domains.

5.3.2 Definition of Primary Estimand

The clinical question of interest is to assess the effect of the active drug on disease progression at Week 116, irrespective of use or initiation of symptomatic treatments for AD, in the absence of a substantial impact of the COVID-19 pandemic.

In alignment with the Addendum to ICH E9, the primary efficacy estimand is described by the following attributes:

- **Target Population**:
  Early (prodromal to mild) AD population as identified by the inclusion and exclusion criteria, see Sections 4.1.1 and 4.1.2 of the study protocols
- **Variable**:
  Change from baseline to Week 116 in Clinical Dementia Rating – Sum of Boxes (CDR-SOB)

- **Treatment**:
  Prescribed study drug including uptitration to the target dose, irrespective of use or initiation of symptomatic treatment for AD
- **Population-level summary**:
  Difference in variable means between treatment arms

Intercurrent events (ICE):

The ICEs are classified into two categories: those that are Study Drug or Condition Related (SDCR) and those that are not (NSDCR). The list of main anticipated ICEs, and their classification as SDCR or NSDCSR, is presented below (Table 3). The final list of ICEs may need to be adapted in case unanticipated ICEs emerge during the study conduct. The classification of each ICE into SDCR or NSDCR will be completed and documented prior to the final database lock.

The ICE of substantial reduction in drug exposure due to the COVID-19 pandemic is defined as 4 or more dose-months (i.e., 16 weeks) of treatment missed due to COVID-19-related reason. One dose-month is defined as 4 weeks of dosing, i.e., one dose with a Q4W dosing frequency (mostly during uptitration) or two doses with a Q2W dosing frequency (at target dose). The threshold (4) on the number of missed dose-months was determined based on the following reasons:

- A 12 weeks' study duration extension was implemented (in protocol amendment version 4) to mitigate the impact of the COVID-19 pandemic. Therefore, treatment interruptions up to 3 dose-months (i.e., 12 weeks) are already accounted for in the study design.
- Based on the half-life of approximately 24 days of gantenerumab, plasma concentrations after 4 months' interruption at the target dose are expected to be below the concentration with the dose of 225 mg Q4W which was shown to be ineffective in studies WN25203 and WN28745
- A 20% difference is the usual acceptability threshold to establish PK bioequivalence. The protocol includes 20 dose-months (80 weeks) at target dose after the up-titration phase. Missing less than 4 dose-months results in overall reduction in drug exposure of less than 20% of the total planned dose.

As a conservative approach, all withdrawals from study treatment due to an AE will be classified as SDCR for the purpose of the primary analysis. This includes withdrawal from study treatment due to suspected or confirmed COVID-19 infection AE because the relationship of these events to the participant condition may be ambiguous.

All SDCR ICEs will be handled with a treatment policy strategy, while NSDCR ICEs will be handled with a hypothetical strategy. The frequencies of ICE will be summarized by treatment arm.

Table 3 Intercurrent Events Impacting Primary Analysis

Intercurrent Event	SDCR/NSDCR	Estimand Approach
Withdrawal from study treatment due to lack of efficacy	SDCR	Treatment Policy
Withdrawal from study treatment due to safety or tolerability reason (NOTE: This will include discontinuation due to AE, incl. suspected or confirmed COVID-19 AEs)	SDCR	Treatment Policy
Withdrawal from study treatment with no informative reason given	SDCR	Treatment Policy
Withdrawal from study treatment due to the COVID-19 pandemic	NSDCR	Hypothetical Strategy
Substantial reduction in drug exposure due to the COVID-19 pandemic (defined as ≥ 4 missed dose-months)	NSDCR	Hypothetical Strategy
Withdrawal from study treatment due to purely administrative reason	NSDCR	Hypothetical Strategy
Death	NSDCR	Hypothetical Strategy
Withdrawal from study treatment due to use or initiation of protocol prohibited medication	SDCR	Treatment Policy
Withdrawal from study treatment due to other SDCR ICEs	SDCR	Treatment Policy

AE = adverse event; COVID-19 = coronavirus disease 2019; NSDCR = Non Study Drug or Condition Related; SDCR = Study Drug or Condition Related

Other ICEs of potential scientific interest, but not impacting the primary analysis, are provided in Table A.2 of Appendix 2.

ICE Derivation

Identification and categorization of the ICEs will be done based on fully blinded data only and will be finalized before database lock.

The number of missed dose-months due to the COVID-19 pandemic will be derived from the standardized eCRF data fields.

All occurrences of “withdrawal from study treatment” ICE, as per Table 3, will be identified and categorized as SDCR/NSDCR based on the standardized reason reported in the eCRF “Study Drug Completion/Early Discontinuation” form. In case of ambiguity (i.e., if the reason for study drug discontinuation as reported in the eCRF is either ‘Protocol deviation’, ‘Withdrawal by subject’, ‘Physician decision’ or ‘Other’), an adjudication committee will review the dedicated eCRF free text field and assign the

withdrawal to a pre-specified ICE and a corresponding SDCR or NSDCR category. The adjudication committee may also introduce additional ICEs to the list, in case no appropriate fit is found in Table 3 or Table A.2 of Appendix 2. The adjudication committee members must not have been involved in the conduct of Studies WN29922 and WN39658 and must not have been exposed to unblinded data from these studies. The members of the adjudication committee must have signed the charter of the adjudication committee, in Appendix 3.

5.3.3 Main Analytical Approach for Primary Estimand and Primary Endpoint

Primary study hypothesis

The primary efficacy analysis for this study will compare the superiority of the active drug over the placebo at Week 116 with a two-sided test corresponding to the following null hypothesis, H_0, and alternative hypothesis, H_1:

$$H_0: \mu_{active} = \mu_{placebo}$$

$$H_1: \mu_{active} \neq \mu_{placebo}$$

Where μ_{active} and $\mu_{placebo}$ are the mean changes from baseline to Week 116 in the CDR-SOB score for each arm.

General strategy to address the ICEs

For the primary estimand, a treatment policy approach will be used for all SDCR ICEs. In line with the clinical question of interest, the aim is to estimate a treatment effect irrespective of the occurrence of these ICEs. This approach is largely in line with the EMA guideline on the clinical investigation of medicines for the treatment of AD (EMA 2018).

All NSDCR ICEs will be handled using a hypothetical approach. The aim is to estimate a treatment effect "as if" the ICE had not happened. Post-ICE outcome values compatible with a hypothetical strategy are not directly observable. Consequently, any observed outcome values after NSDCR ICEs will be removed and treated as missing data for the analysis purpose.

For participants with multiple ICEs, the type of the first ICE will determine the strategy to be considered.

Missing data assumptions for the primary estimator

For intermittent missing data (i.e., for participants with non-missing Week 116 data but missing data at other visits), missing data not associated with an ICE (e.g., for participants who had completed W104 visit before protocol v4), and for missing data after NSDCR ICEs (handled with a hypothetical strategy), the missing data are assumed

to be similar to those from the other participants in the same treatment group with no such missing data. This is compatible with a missing-at-random (MAR) assumption.

All observed data after SDCR ICEs will be included in the analysis. If data after SDCR ICEs are missing, they will be assumed to be similar to those in the placebo group for both study arms. Specifically, data will be imputed based on the placebo arm using reference based imputation with a Copy Increments from Reference (CIR) assumption (Carpenter et al, 2013 and Cro et al, 2020). This approach appears conservative yet plausible for the study drug. CIR assumes that changes in the primary endpoint after the ICE in a participant randomized to active drug can be represented by, i.e., imputed from, that of participants randomized to placebo. It therefore assumes no treatment effect after the ICE. In the placebo arm, this is compatible with a MAR assumption whereas in the active treatment arm, the imputation is under a Missing Not At Random (MNAR) assumption.

Further details about the implementation of the missing data imputation are provided below. Sensitivity analyses for the missing data assumptions are discussed in Section 5.3.4.

Description of the primary estimator

The primary estimator will be applied to the ITT analysis set (see Table 2) and it will be implemented using four steps. First, an imputation model will be fitted to the data. Second, imputation of missing data will be performed based on the parameter estimates from the imputation model. Third, the completed data will be analyzed using an analysis of covariance (ANCOVA) model. Finally, inference will be performed based on resampling techniques. All four steps are described and justified below. A draft manuscript with a more detailed justification of the statistical methodology and supportive simulations is available in arXiv (Wolbers et al. 2021).

1. Imputation model

The imputation model is a mixed effects model for repeated measures (MMRM) with the longitudinally assessed change from baseline in CDR-SOB as the dependent variable. Its purpose is to estimate mean trajectories and covariance matrices of longitudinal outcomes in the placebo and active treatment arms, respectively, while subjects remain on their randomized treatment. Therefore, all data after withdrawal from study treatment will be removed and considered as missing for the purpose of estimating the imputation model, and for this purpose only. If we did not exclude these data, then the imputation model would estimate mean trajectories based on a mixture of observed pre- and post-discontinuation data. These would not be compatible with the CIR assumption employed in the subsequent imputation step, which requires combining mean trajectories while on active treatment up the ICE with increments while on placebo thereafter, respectively.

The imputation model includes the following covariates: treatment group, visit, and treatment-by-visit interaction, baseline CDR-SOB score and baseline CDR-SOB score - by-visit interaction, baseline ADAS-Cog 13 total score, baseline ADCS-ADL total score and the randomization stratification factors namely: disease stage (from eCRF), geographic region (from the IxRS), the use of AD medication at baseline (from eCRF) and the APOE ε4 status (from the Vendor). An unstructured variance-covariance structure will be applied to model the within-subject errors across visits. If the model fails to converge, then a heterogeneous Toeplitz covariance structure will be used instead and if this still fails, then a compound symmetry covariance structure will be used.

Imputations will be based on restricted maximum likelihood (REML) estimation of the regression and covariance parameters from the imputation model (von Hippel and Bartlett 2020; Wang and Robins 1998).

2. Imputation step

The imputation model implies a marginal multivariate normal distribution of the longitudinal outcome values across all visits based on a participant's assigned treatment arm and covariate values. This marginal imputation distribution will be used for all participants in the placebo arm and all participants in the active treatment arm without an SDCR ICE. For participants in the active treatment arm with an SDCR ICE, the mean of the marginal imputation distribution for outcomes after the SDCR ICE will be modified as per the CIR assumption (Carpenter et al, 2013).

For each participant, the conditional imputation distribution of their missing outcome values is defined as the marginal imputation distribution conditional on the participant's observed outcomes (including observed post-SDCR ICE outcome assessments). A single deterministic imputation using the conditional mean from the conditional imputation distribution for each participant with missing outcomes will be used.

3. Analysis step

The completed data (using conditional mean imputation as described above) will be analyzed using an ANCOVA model with the change from baseline in CDR-SOB at the Week 116 visit as the dependent variable. This analysis model includes treatment group as the primary covariate with adjustment for the same set of covariates as for the imputation model described above, namely baseline CDR-SOB score, baseline ADAS-Cog 13 total score, baseline ADCS-ADL total score and the randomization stratification factors namely: disease stage (from eCRF), geographic region (from the IxRS), the use of AD medication at baseline (from eCRF) and the APOE ε4 status (from the Vendor). The primary treatment effect estimator is defined as the regression coefficient associated with the treatment group. The treatment effect at the other visits will be estimated in the same way.

Importantly, ANCOVA is applied to a complete dataset after appropriate missing data imputation. For complete data, ANCOVA applied to outcomes from a single visit is equivalent to a more complex MMRM model. It can be demonstrated that it leads to identical parameter estimates as a corresponding MMRM model with an arbitrary covariance structure if separate regression coefficients are estimated at different visits for all covariates (Amemiya 1985, p. 197).

4. Inference step

Inference will be based on resampling techniques as recommended by von Hippel and Bartlett 2020. Specifically, the jackknife will be used to estimate the standard error of the primary treatment effect estimator and the test of the primary statistical hypothesis will be based on the corresponding *Z*-score (Efron and Tibshirani, 1994). Compared to other resampling techniques, the jackknife has the advantage of providing a deterministic standard error estimate and, hence, removing any simulation randomness from the procedure.

5.3.3.1 Software Implementation and Validation

The reference based imputation methodology will be implemented by an internally developed R package "rbmi" ("reference-based multiple imputation"). The package will comply with the ICH guidance document "ICH E 9: Statistical principles for clinical trials" which states that: "The computer software used for data management and statistical analysis should be reliable, and documentation of appropriate software testing procedures should be available."

The testing strategy for the package consists of defining and documenting the expected input and output of each function and implementing unit tests to prove that the package performs as expected. All implemented methods will be recorded and referenced against the literature with unit tests and simulations put in place to show that known values can be recovered as well as showing consistency with similar software from other languages (most notably the "5-Macros" implemented by the Drug Information Association Scientific Working Group on Estimands and Missing Data in SAS).

The package, including all documentation and testing materials, will be publicly released on GitHub.com and submitted to the publicly accessible CRAN repository (cran.r-project.org/) to allow for unrestricted access and enable public scrutiny of the code and methods.

Finally, as part of Roche internal process for the validation of R packages, the package will also be submitted to a third party for independent review prior to being installed on our system.

5.3.4 Sensitivity Analyses for Primary Endpoint

Impact of COVID-19 pandemic

The following sensitivity analyses will be performed to evaluate the impact of the COVID-19 pandemic:

- Vary threshold on number of missed doses due to the pandemic in the definition of "substantial reduction in drug exposure" ICE. The 'substantial reduction in drug exposure' ICE is defined with a threshold ≥ 4 dose- months. A sensitivity analysis will be performed using different thresholds: 1, 2, 3, 5 and 6 dose-months. All other aspects of the primary estimator will remain the same.
- Exclude participants based on site closure information. In this analysis, all participants enrolled before a site closure due to the pandemic will be removed from the analysis population. In alignment with primary estimands, only site closure of 16 weeks or more during the double-blind treatment period and without any access to study drug (no home nursing) will be considered. Participants excluded from this analysis can be identified using baseline data only: randomization date and site number. The site closure information is an administrative site level information, independent of the conduct of the trial, collected using the eCRF for the purpose of this study and analysis. All COVID-19-related ICE for remaining participants will be handled with a treatment policy strategy. All other aspects of the primary estimator will remain the same.
- Remote scale administration. Remote scale administration was authorized in exceptional cases at Weeks 104 and 116 visits due to COVID-19 related restrictions. In this analysis, all CDR-SOB assessments performed remotely will be excluded from the analysis and treated as missing data. All other aspects of the primary estimator will remain the same.
- A subgroup analysis based on the date of randomization. This will allows estimating the treatment effect for subgroups of participants randomized at least 12 months before the COVID pandemic, in between 6 to 12 months prior to the COVID pandemic and within less than 6 months from the COVID pandemic (see section 5.3.5.1 for an exact definition of each subgroup).

Impact of missing data handling methods

The following sensitivity analyses will be performed to evaluate the impact of missing data handling method:

- Tipping point analysis

  This analysis stress tests the CIR assumption by imputing worse outcomes after SDRC ICEs in the active treatment arm than predicted by the CIR assumption. This will be implemented via a marginal δ-approach as described in the user manual to the "5-Macros" and in Cro et al, 2020. Specifically, the imputation step will be performed as for the primary estimator and, after imputation is completed, a

constant δ will be added to the imputed week 116 outcomes occurring after SDCR ICEs in the active treatment arm. The subsequent analysis step of these δ-adjusted imputed datasets is as for the primary estimator.

To determine the tipping point, the constant δ will be increased in small steps starting from a value of 0 (corresponding to the primary estimator). The tipping point will then be defined as the value of δ at which the p-value for the treatment effect estimator first becomes greater than 5%.

– MMRM

This analysis aims to provide a reference point analysis method described in early versions of the protocol (up to version 4) and to other external analyses where MMRM was considered the default and primary analysis. All data following NSDCR withdrawal from study treatment ICE will be excluded from the analysis and treated as missing data. All the other available outcome data, including data collected after treatment discontinuation and due to SDCR, will be used in the analysis. There will be no missing data imputation or consideration for any other intercurrent events.

The model will include the following covariates: treatment group, visit, and treatment-by-visit interaction, baseline CDR-SOB score and baseline CDR-SOB score -by-visit interaction, baseline ADAS-Cog 13 total score, baseline ADCS-ADL total score and the randomization stratification factors namely: disease stage (from eCRF), geographic region (from the IxRS), the use of AD medication at baseline (from eCRF) and the APOE ε4 status (from the Vendor). An unstructured variance-covariance structure will be applied to model the within-subject errors across visits. If the model fails to converge, then a heterogeneous Toeplitz covariance structure will be used instead and if this still fails, then a compound symmetry covariance structure will be used.

Impact of potential outliers or extreme observations

In order to assess the impact of a potentially small number of “extreme observations” or “outlier points” (i.e. rapid progressors) on the treatment effect, the ANCOVA analysis model will be replaced by a robust linear regression. Robust regression will produce treatment effect estimates less contaminated by highly influential observations. Specifically, robust regression using M estimation and Huber’s psi-function will be used. Standard errors and confidence intervals will be based on jacknife or bootstrap resampling as described previously.

5.3.5 Supplementary Analyses for Primary Endpoint

5.3.5.1 Subgroup Analyses for Primary Endpoint

The generalizability of the CDR-SOB results when comparing the active drug arm to the placebo arm will be investigated by estimating the treatment effect in the following subgroups:

- Demographics:
  - Age, less than 65 years old versus 65 years and more
  - Sex
  - Geographic Region
- Baseline disease severity:
  - 'MMSE ≥ 24 and CDR-GS = 0.5' vs 'MMSE < 24 or CDR-GS > 0.5'
  - CDR-GS = 0.5 vs CDR-GS > 0.5
  - Prodromal vs Mild (as per eCRF)
- APOE ε4 genotype
  - Carrier/Non Carrier
- Use of symptomatic AD medication at baseline
- Participation in Tau-PET and amyloid-PET substudies
- Randomization date, three subgroups defined by the following dates:
  - *before* 11 March 2019
  - *in between* (and including) 11 March 2019 and 1 October 2019
  - *after* 1 October 2019

Summaries of CDR-SOB by these subgroups will be provided in forest plots.

5.3.5.2 Other Supplementary Analyses for Primary Endpoint(s)

Two supplementary estimands will be evaluated. The analysis for the supplementary estimands will be conducted only on the primary endpoint.

Treatment policy estimand

All ICEs will be handled with a treatment policy strategy regardless of whether being SDCR or NSDCR. All observed data will be included regardless of occurrence of any ICE. Missing values will be imputed with the method used in the primary estimator for missing data following a treatment policy ICE, see Section 5.3.3. Note that the attributes of population, variables, treatment and population level summary will remain the same as for the primary estimand.

Concomitant AD treatment estimand

In this supplementary analysis, the treatment effect will be evaluated in the hypothetical scenario that no post-baseline initiation or modification of the use of other approved AD medication has happened.

All attributes of this estimand except Treatment will be identical as for the primary estimator. The treatment attribute will be: "Prescribed study drug including uptitration to the target dose, irrespective of concomitant use of symptomatic treatment for AD at baseline, but assuming no initiation or change in symptomatic treatment after baseline". In this supplementary analysis, all data following ICEs "Starting another treatment for AD" and "Changing the dose of a symptomatic treatment for AD" will be analyzed following a hypothetical strategy. The analysis methods will be the same as described for the primary estimand.

Clinically evident decline: a Progressor analysis

In this supplementary analysis, the outcome variable will be a binary event of CDR-SOB progression at Week 116. Progression will be defined as an increase in CDR-SOB greater than or equal to a threshold *x* at Week 116. According to the current literature, meaningful progression on the CDR-SOB ranges from 1–2.5 points in an early AD population (Andrews et al. 2019; Lansdall et al. 2019). A cumulative distribution function (CDF) plot will be generated to explore graphically the proportion of patients that achieve a given score change ("x") on the CDR-SOB at the individual level by treatment arm at week 116. The analysis of progression will be based on the same imputed dataset as for the primary estimand and corresponding standard errors and confidence intervals will be calculated using the bootstrap or the jackknife as previously described.

In addition, logistic regression, Kaplan-Meier and the Cox proportional hazard model will be used to estimate other relevant summary statistics such as odds ratio, risk ratio and time to event summaries. These models will have the progression at Week 116, or time to first progression as the dependent variable and may include a similar set of covariates as for the primary estimator.

5.4 SECONDARY ENDPOINTS ANALYSES

The primary estimand's analysis strategy will be applied to secondary endpoints listed in Table 4. For all continuous secondary endpoints, the estimator also remains unchanged. For all continuous secondary endpoints, the analysis model will include the baseline score of the secondary endpoint as a covariate, in addition to a similar set of covariates as for the primary estimator.

In the event of a significant effect on secondary endpoints and where appropriate, descriptive CDF plots will be generated to explore the effect of treatment on the measure of interest at the individual level.

In the following, confirmatory secondary endpoints refer to endpoints included in the type I error control procedure. Other important secondary endpoints not subject to the type I error control procedure are considered as supportive secondary endpoints.

Table 4 Secondary Endpoints

Secondary efficacy endpoint	Confirmatory	Type
Alzheimer's Disease Assessment Scale, Cognitive subscale, 13-item (ADAS-Cog 13)	yes	Continuous
Alzheimer's Disease Cooperative Study, Activities of Daily Living scale (ADCS-ADL) total score	yes	Continuous
Functional Activities Questionnaire (FAQ)	yes	Continuous
Mini Mental State Examination (MMSE)	no	Continuous
Alzheimer's Disease Assessment Scale, Cognitive subscale, 11-item (ADAS-Cog 11)	no	Continuous
Coding (Digit Symbol Substitution Test [DSST])	no	Continuous
Verbal Fluency Task	no	Continuous
Alzheimer's Disease Cooperative Study, Activities of Daily Living scale (ADCS-ADL) instrumental score	no	Continuous

ADAS-Cog 13= Alzheimer's Disease Assessment Scale, Cognitive subscale, 13-item; ADCS-ADL= Alzheimer's Disease Cooperative Study, Activities of Daily Living scale; ADAS-Cog 11= Alzheimer's Disease Assessment Scale, Cognitive subscale; DSST= Digit Symbol Substitution Test; FAQ= Functional Activities Questionnaire; MMSE= Mini Mental State Examination.

5.4.1 Confirmatory Secondary Endpoints

The confirmatory secondary endpoints are provided to increase the confidence in the treatment effect observed on the primary endpoint. For these confirmatory secondary endpoints, the analysis method will be the same as for the primary endpoint. All estimands attributes except Variable (i.e., Target population, Treatment, Population-level summary) will be identical as for the primary estimator (see Section 5.3.1). The same ICE and analysis methods will be used, see Section 5.3.3.

The method for controlling the overall Type I error is described in section 5.1.

5.4.1.1 Alzheimer's Disease Assessment Scale, Cognitive Subscale, 11- item and 13-Item (ADAS-Cog 11/ ADAS-Cog 13)

The ADAS-Cog is the most frequently used scale to assess cognition in clinical trials for mild to moderate AD dementia (Rozzini et al. 2007; Connor and Sabbagh 2008; Ihl et al. 2012). More specifically, the ADAS-Cog is a participant-based assessment that measures learning and memory, language production, language comprehension,

constructional praxis, ideational praxis, and orientation. The modified version will be used; it has 13 items and includes the addition of delayed word recall and a number of cancellation subtests, as well as use of only one trial for word recognition (Mohs et al. 1997). Equivalent alternate forms of the word recall, word recognition, and number cancellation subtests will be used in successive test administrations. The ADAS-Cog 11 and 13 will be used in this study, with ADAS-Cog 13 considered as a confirmatory secondary endpoint. Individual item scores are based on errors and generally range from 1 to 5, although some items have smaller or larger score ranges. The ADAS-Cog 13 total score ranges from 0-85, with higher scores reflecting greater impairment. It takes approximately 45 min to administer the ADAS-Cog 13.

5.4.1.2 Alzheimer's Disease Cooperative Study, Activities of Daily Living Scale (ADCS-ADL), Total Score

The ADCS-ADL (Galasko et al. 1997) is the scale most widely used to assess functional outcome in participants with AD (Vellas et al. 2008). The ADCS-ADL is a 23-item informant-based questionnaire that covers both basic activities of daily living (ADL) (e.g., eating and toileting) and more complex ADL or instrumental ADL (e.g., using the telephone, managing finances, preparing a meal). It has a 4-week recall period. Total scores range from 0-78, with higher scores indicating better functioning.

5.4.1.3 Functional Activities Questionnaire (FAQ)

The FAQ (Pfeffer et al. 1982) is an informant-based measure of functional abilities. Informants provide performance ratings of the target person on ten complex higher-order activities. The FAQ is a 30-point scale, the higher the score the worse the performance.

5.4.2 Supportive Secondary Endpoints

For context, additional clinical endpoints collected longitudinally in the studies will be provided (see Table 4). The Sponsor proposes not to rank these hierarchically as for confirmatory secondary endpoints.

5.4.2.1 Mini Mental State Examination (MMSE)

The MMSE is a set of standardized questions used to evaluate possible cognitive impairment and help stage the severity level of this impairment (Folstein et al. 1975). The questions target six areas: orientation, registration, attention, short-term recall, language, and constructional praxis/visuospatial abilities. The MMSE is a participant-based assessment.

5.4.2.2 Digit Symbol Substitution Test (DSST)

Coding, also called Digit Symbol Substitution Test (or DSST), is a subtest from the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV; Wechsler 2008). Coding is a participant-based assessment that measures speed of processing and associative memory. The test is known to be sensitive to disease progression (Lezak et al. 2004). The 120-second version of the test will be used in this study.

5.4.2.3 Verbal Fluency Task

The category verbal fluency (e.g., animals) is a participant-based assessment that measures speed and flexibility of verbal thought. Verbal fluency tests are sensitive tools for detecting dementia (Pasquier et al. 1995; Lezak et al. 2004) and for monitoring decline over time (Clark et al. 2009).

5.4.2.4 Alzheimer's Disease Cooperative Study, Activities of Daily Living Scale (ADCS-ADL), Instrumental Score

See Section 5.4.1.2.

5.4.3 COVID-19 related Sensitivity Analyses for Secondary Endpoints

During the COVID-19 pandemic, many countries took movements' restriction policy. Among the clinical outcomes collected in the study, some questionnaires may be particularly impacted. These questionnaires include items describing actions that are strongly constrained or prohibited by restriction policies.

We define modified versions of the total score for these scales. These modified scales scores may be used to perform sensitivity analysis aiming at understanding and mitigating the impact of the COVID-19 pandemic on study results and interpretation, in line with the primary clinical question of interest.

5.4.3.1 ADCS-ADL COVID-19 Modified Total Score

The original ADCS-ADL is a 23 item scale with a total score range of 0-78. The following items were identified as being particularly impacted by the pandemic related restrictions:

- Item 2: Optimal walking performance, maximum 3 points
- Item 15: Optimal performance getting around/travelling outside the home, maximum 4 points
- Item 16a/b: Shopping trips - selecting items and paying without supervision, maximum 4 points
- Item 18: Left away from home, maximum 3 point

A sensitivity analysis may be conducted, using a modified version of the ADCS-ADL total score after removing of these four items, resulting in a 19-item scale with a score range of 0-64. This alternative version will be referred to as "ADCS-ADL COVID-19 modified total score".

5.4.3.2 FAQ COVID-19 Modified Total Score

The original FAQ is a 10-item scale with a score range of 0-30. The following items were identified as being particularly impacted by the pandemic related restrictions:

- Item 3: Shopping alone, maximum 3 points
- Item 10: Travelling outside of the neighborhood, maximum 3 points

A sensitivity analysis may be conducted, using a modified version of the FAQ total score after removing of these 2 items, resulting in an 8-item scale with a score range of 0-24. This alternative version will be referred to as “FAQ COVID-19 modified total score”.

5.5 EXPLORATORY ENDPOINT(S) ANALYSIS

The primary estimand’s analysis strategy will be applied to exploratory endpoints listed in Table 5. For continuous endpoints, the same estimator as for the Primary endpoint will be used. For binary endpoints, logistic regression, Kaplan-Meier and Cox proportional hazard model may be used to estimate treatment effect using relevant summary statistics such as odds ratio, risk ratio and time to event summaries. These analyses will be based on the same imputed dataset as for the continuous version of the endpoint. Corresponding standard errors and confidence intervals will be calculated using the bootstrap or the jackknife as previously described.

Table 5 Exploratory Endpoints

Exploratory efficacy endpoint	Type
Clinical Dementia Rating-Global Score (CDR-GS)	Continuous / Binary
CDR-Individual Components	Continuous
Dependency Level, as assessed by the Alzheimer disease cooperative study - activities of daily living (ADCS-ADL) score	Continuous / Binary
Integrated AD Rating Scale (iADRS)	Continuous
AD Composite Score (ADCOMS)	Continuous
Quality of Life–Alzheimer’s Disease (QoL-AD)	Continuous
Neuropsychiatric Inventory Questionnaire (NPI-Q)	Continuous
Zarit Caregiver Interview–Alzheimer’s Disease (ZCI-AD)	Continuous
Resource Utilization in Dementia Scale–Lite (RUD-Lite)	Continuous
EuroQoL–5 Dimensions visual analog scale (EQ-5D VAS)	Continuous

ADCS-ADL = Alzheimer disease cooperative study-activities of daily living; ADCOMS = AD Composite Score; CDR-GS =Clinical Dementia Rating-Global Score; EQ-5D= EuroQoL–5 Dimensions; iADRS = Integrated AD Rating Scale; NPI-Q= Neuropsychiatric Inventory Questionnaire ; QoL-AD =Quality of Life–Alzheimer’s Disease; ZCI-AD=Zarit Caregiver Interview–Alzheimer’s Disease.

5.5.1.1 Clinical Dementia Rating–Global Score (CDR-GS) and Individual Components of the CDR scale

The Washington University CDR is a global assessment instrument that yields global scores (GS) and sum of boxes (SOB) scores. The CDR is derived from a semi-structured interview with the participant and an appropriate informant, and it rates impairment in six categories (Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care) on a 5-point scale for which 0 = no impairment, 0.5 = questionable impairment, and 1, 2, and 3 = mild, moderate, and severe impairment, respectively. From the six individual category ratings, or box scores, the CDR-GS is established by clinical scoring rules, for which CDR 0 = no dementia and CDR 0.5, 1, 2, or 3 = questionable, mild, moderate, or severe dementia, respectively (Morris 1993).

The CDR-GS may be analyzed as a binary endpoint. The dichotomization will be based on the change from baseline to week 116 (>0 versus <=0). The CDR-GS may also be analyzed as a time-to-event endpoint. The event time will be defined as the earliest time point with change from baseline >0.

With the COVID-19 pandemic, several countries took movement restrictions policies that raised concerns about the validity of CDR scale in this context. The Community Affairs and the Home and Hobbies explore functions that are constrained by movement restrictions. These domains might be more specifically impacted than others during pandemic periods.

5.5.1.2 Dependence Level Assessed by the ADCS-ADL Score

To calculate dependence levels, scores on the ADCS-ADL can be transformed into discrete levels of disability via an algorithm developed initially by Kahle-Wrobleski (2015). Items from the ADSC-ADL were mapped to 6 levels of dependence derived from the Dependence Scale (Zhu et al., 2009), ranging from Level 0: no impairment in instrumental or basic ADLs to Level 5: complete incontinence. Four subscales were used to aid the construction of dependence levels, including bADLs, domestic/household activities, communication/engagement and outside activities. The mapping of items to dependence levels was validated using additional clinical and economic measures.

A revised algorithm, developed to a) remove ambiguity regarding the contribution of some items and b) add clarity on the handling of missing data, will be used to calculate the dependence levels. Progression to greater levels of dependence is indicative of disease progression and is informative for a variety of care providers and stakeholders. This algorithm will be provided before database lock for interim analysis.

5.5.1.3 Integrated AD Rating Scale (iADRS)

The iADRS is a composite of cognition and function that combines scores from the ADAS-Cog-13 (cognition) and the instrumental component of the ADCS-ADL (function)

(Wessels et al., 2018). A sum score of the total scores of both components is calculated (ADAS-Cog is reversed) using the following formula:

iADRS = [-(ADAS-Cog13) + 85] + ADCS-iADL.

Total score range from 0 to 141.

5.5.1.4 AD Composite Score (ADCOMS)

The ADCOMS was developed to assess cognition and function in early stages of AD. It is a composite score that combines 12 items from existing AD measures, specifically the ADAS-Cog (Delayed word recall, Orientation, Word recognition, Word finding difficulty), MMSE (Orientation time and Constructional praxis) and all CDR-SB items (Wang et al., 2016). The ADCOMS score was built using a linear longitudinal model to characterize the relationship between disease progression and the individual items from existing AD clinical scales. A PLS regression procedure was used to identify individual clinical scale items that represent AD-related clinical decline over time to calculate their respective weighting factors. The resulting composite ADCOMS score is a weighted linear combination of the individual scale items selected in the fitted PLS model. Items with small contribution to the PLS model were removed according to Wold's criterion (a Variable Importance of Projection below 0.8). Total score range from 0 to 1.97, with lower scores indicating greater impairment.

5.5.1.5 Quality of Life–Alzheimer's Disease (QoL-AD)

The Quality of Life-Alzheimer's Disease (QoL-AD) was developed to assess quality of life (QoL) in participants who have dementia (Logsdon et al. 1999, Logsdon et al 2002). The QoL-AD consists of 13 items covering aspects of participants' relationships with friends and family, physical condition, mood, concerns about finances, and overall assessment of QoL. The total score is the sum of the 13 items and ranges from 13 to 52, with higher scores indicating better health-related QoL. In this study, the QoL-AD will be administered in a standardized, structured interview format to participants by investigative staff in order to gather participant responses about QoL. The study partner will also complete the study partner version of the questionnaire to enable proxy responses from the study partner.

5.5.1.6 Neuropsychiatric Inventory Questionnaire

The Neuropsychiatric Inventory-Questionnaire (NPI-Q) (Kaufer et al. 2000) was developed to assess a wide range of behaviors encountered in dementia participants, to provide a means of distinguishing severity of behavioral changes, and to facilitate rapid behavioral assessment through the use of screening questions. It is an informant-based instrument in which 12 behavioral domains are evaluated. The recall period is the past month, and severity scores range from 0 to 36, with higher scores indicating greater severity. The study partner's distress portion of the scale was not used in this study.

5.5.1.7 Zarit Caregiver Interview–Alzheimer's Disease (ZCI-AD)

The Zarit Caregiver Interview-Alzheimer's Disease (ZCI-AD) is a modified version of the Zarit Burden Interview 22-item version, which was originally designed to reflect the stresses experienced by caregivers for people with dementia (Zarit and Zarit 1990). The modified version includes modifications in item and title wording (e.g., removal of "your relative " to refer directly to the participant, removal of "burden" from title), inclusion of additional items, the use of 11-point numerical rating scales for each item and a 4 week recall period. The ZCI-AD measure consists of 27 items covering 13 domains (i.e. humanistic impact domain (14 items) including the domains physical (3 items), emotional (4 items), social (3 items), and daily life (4 items), and the additional domains exhaustion (2 items), dependence (2 items), worry (2 items), role perception (3 items), financial impact (1 items), difficulty with medication (1 item), overall difficulty of caregiving (1 item), and sadness (1 item)). The ZCI-AD is completed by the study partner without involvement from the site staff. The ZCI-AD is scored on a domain level with each domain score ranging from 0 to 100 with higher scores indicating higher level of impact. The ZCI-AD has been validated in prodromal, mild and moderate stages of AD (Le Scouiller et al., in progress).

5.5.1.8 Resource Utilization in Dementia Scale–Lite (RUD-Lite)

The Resource Utilization in Dementia (RUD) scale (Wimo et al. 2003) aims to document formal and informal resource use in a clinical trial setting. The RUD-Lite captures the most important elements in dementia care: accommodation, informal care, hospitalizations, and community care services. Information on study partner sociodemographics in addition to working status and effect on productivity will be collected. The amount of informal care will be collected according to three types of care: personal ADL, instrumental ADL, and supervision. Data on accommodation and temporary changes in accommodation during the last month and the duration of these will be collected according to four levels of accommodation: own home, intermediate forms of accommodation, dementia-specific residential accommodation, and nursing home. Resource utilization will be recorded as the number of nights spent in different types of hospital wards, the number of visits to the most common types of outpatient care, and the number of visits in community care services.

5.5.1.9 EuroQoL–5 Dimensions visual analog scale (EQ-5D VAS)

The EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) self report is a widely used patient reported measure to assess health status (EuroQol Group 1990). There are two parts to the EQ-5D-5L which asks the individual to select a response that best describes their health 'today.' The first part consists of a five-item health state profile used to assess mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Items are rated on a 5-point Likert scale ranging from 1 (no problems) to 5 (extreme problems/unable to do). The second part consists of a visual analogue scale (EQ-5D VAS) that measures health state, ranging from 0 (worst health imaginable) to 100 (best health imaginable). A total index value can be calculated using

published weighting (EuroQoL website) typically ranging from 0 (equivalent to dead; negative values representing worse than dead) to 1 (full health). The EQ-5D-5L takes a few minutes to complete and will be used in this study for informing pharmacoeconomic evaluations. The following two versions will be used in this study:

- EQ-5D-5L Proxy, Version 1: The study partner (the proxy) is asked to rate the participant's health-related QoL in his or her (the proxy's) opinion.
- EQ-5D-5L, Self-Complete Version: The study partner is asked to rate his or her own health-related QoL.

The CSR will report only the EQ-5D VAS, while the EQ-5D-5L itself will be analyzed and reported separately.

5.6 SAFETY ANALYSES

Descriptive statistics will be used to analyze all safety data collected in the double-blind treatment period in the safety-evaluable analysis population, unless otherwise specified. Safety data collected during the safety follow-up of the double-blind treatment will also be included but may be summarized in separate tables. For participants entering the open-label extension (OLE) period, all events reported on or after the day of first study drug intake and up to the day before the first dose in the OLE period will be analyzed for the double-blind treatment period. Safety data collected in the OLE period of the studies will be reported separately.

Safety analyses will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, MRI findings, changes in vital signs and ECGs, and changes in C-SSRS scores.

5.6.1 Extent of Exposure

Exposure to study drug information will be descriptively summarized by treatment as follows:

- Treatment duration (in weeks)
- Total number of administrations
- Total cumulative dose (mg)
- Frequencies of participants in each dose level

5.6.2 Adverse Events

All verbatim AEs terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version that is current at the time of the analysis (Version 24.0 or higher), and AE severity will be graded according to the scale defined in Table 5 in Section 5.3.3 of the study protocol (mild/moderate/severe). For each treatment group, the frequency of each AE preferred term will be defined as the number of participants experiencing at least one occurrence of the event. Each table will present the overall number and percentage of participants experiencing at least one AE and the total

number of AEs reported. Percentages will be based on the number of participants in the safety-evaluable analysis population. In summary tables, AEs will be sorted by body system (in decreasing order of overall incidence), then by preferred term (in decreasing order of overall incidence).

The following safety information will be summarized by treatment group for the double-blind treatment period:

- AEs, AEs by intensity, AEs related to study drug
- Deaths
- SAEs, SAEs by intensity, SAEs related to study drug
- AEs leading to discontinuation of study treatment
- AEs leading to dose modifications (dose interruption, dose reduction, no up-titration)
- Protocol-specified adverse events of special interest (AESI)
- Injection site reaction (ISR) signs and symptoms
- Systemic injection reactions (AEs with “systemic reaction” selected)

The impact of the COVID-19 pandemic on the safety data will be assessed by reviewing the following:

- Confirmed or suspected COVID-19 AEs
- AEs associated with COVID-19
- Potential long COVID-19 symptoms

The following data handling rules will be applied for all AE summary tables:

- Events that are missing both at onset and at end dates will be considered to have started after the first dose of study drug and the duration will be set to missing.
- If the onset date is missing, and the end date is on or after the first dosing date or unresolved or missing, then the event will be considered to have started after the first dose of study drug.

The following data handling rules will also be applied for specific tables:

- An AE will be included in the summary table of AEs leading to study drug discontinuation if the “action taken with blinded gantenerumab” drop-down menu on the AE eCRF is checked “drug withdrawn”.
- In the summary table of AEs by intensity, if a participant has more than one occurrence of an event, the event with the most severe intensity will be counted. If the intensity of an AE is missing, then the AE will be included only in the total number of events column, and not in the count of participants with the event by intensity.

- In the summary table of AEs by relationship to study drug, if a participant has more than one occurrence of an event, the related event will be counted if applicable. If the relationship of an AE is missing, then the AE will be included only in the total number of events column, and not in the count of participants with the event by relationship

5.6.3 Magnetic Resonance Imaging Safety Findings

ARIA-E and ARIA-H are identified risks associated with gantenerumab. Sites were asked to capture all ARIAs as AEs in the eCRF that met any of the following criteria:

- Symptomatic ARIA-E (i.e., accompanied by CNS symptoms), and/or
- ARIA findings that result in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation), and/or
- Findings that are otherwise clinically significant in the investigator's judgment

As not every MRI finding of ARIA qualifies as an AE, ARIA events for ARIA analyses will be identified from MRI data. Based on MRI data, the incidence, severity (based on the Barkhof Grand Total Score [BGTS]), and timing of ARIA-E and ARIA-H will be summarized by treatment group and within this also by APOE ε4 genotype (carrier vs. non-carrier) and by dose level. The timing of ARIA-E and ARIA-H will be summarized by descriptive statistics and Kaplan-Meier methods. Recurrence of ARIA-E will be summarized by treatment group and within this also by APOE ε4 genotype (carrier vs. non-carrier). ARIA-E associated with CNS symptoms (see Section 5.6.3.1) and with serious CNS symptoms will be summarized by treatment group and within this also by APOE ε4 genotype. Temporal co-occurrence of ARIA-E and ARIA-H will be summarized by treatment group and within this also by APOE ε4 genotype. Temporal co-occurrence is defined as an MRI scan showing new ARIA-H that occurs between ARIA-E onset and resolution (inclusive), irrespective of the brain region.

5.6.3.1 CNS Symptoms Temporally Associated with ARIA-E MRI Findings

CNS symptoms temporally associated with ARIA-E are defined as onset or worsening of CNS symptom(s) that is/are temporally associated with ARIA-E MRI findings. CNS symptoms experienced by the participant that are new or worsened since the last MRI without ARIA-E are collected in a CNS Symptoms Request Form before the MRI takes place at a visit. To identify CNS symptoms temporally associated with ARIA-E MRI findings, the following definitions will be used:

NEW CNS symptoms: If there is any AE reported in the eCRF with 'Reported on the MRI CNS symptoms request form' = Y that is [new since date of most recent MRI scan showing no ARIA-E findings] AND is [ongoing or ends between the date of most recent site visit prior to date of MRI scan showing new ARIA-E (MRI) and date of MRI scan showing ARIA-E resolution (MRI)] then ARIA-E should be classified as associated with CNS symptoms

OR

WORSENED CNS symptoms: If there is any AE reported in the eCRF with 'Reported on the MRI CNS symptom request form' = Y that is [started before the date of most recent MRI scan showing no ARIA-E findings] AND is [ongoing or ends between the date of most recent site visit prior to date of MRI scan showing new ARIA-E (MRI) and date of MRI scan showing ARIA-E resolution from MRI data] AND [there is an increase in severity grading] then ARIA-E should be classified as associated with CNS symptoms.

The CNS symptoms temporally associated with ARIA-E MRI findings will be listed and summarized by treatment group and within this also by APOE ε4 genotype (carrier vs. non-carrier).

5.6.4 Laboratory Data

Laboratory data will be summarized by treatment group for each assessment visit using descriptive statistics of absolute values, change from baseline values, and percentage change from baseline. In addition, the frequency of patients with abnormal laboratory values will be summarized by treatment group, visit and baseline status.

5.6.5 Vital Signs

Vital signs assessments include systolic blood pressure, diastolic blood pressure, and pulse rate measured throughout the study. Vital sign measurements will be summarized by treatment group for each assessment visit using descriptive statistics of absolute values, change from baseline values, and percentage change from baseline. In addition, the frequency of patients with abnormal results will be summarized by treatment group, visit and baseline status.

5.6.6 ECGs

ECG data will be summarized by treatment group for each assessment visit using descriptive statistics of absolute values, change from baseline values, and percentage change from baseline for the following parameters:

- Heart rate
- QRS duration
- RR interval
- PR interval
- QT interval

In addition, ECG overall interpretations will be summarized by treatment group and visit.

5.6.7 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS (http://www.cssrs.columbia.edu) is an assessment tool used to assess the lifetime suicidality of a participant (C-SSRS at baseline) as well as any new instances of suicidality (C-SSRS since last visit). The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual or potential lethality.

Suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent will be summarized by treatment group at each assessment visit. In addition, change from baseline to worst post-baseline assessment in suicidality categories will be summarized by treatment group.

5.7 OTHER ANALYSES

5.7.1 Summaries of Conduct of Study

The summary of study conduct will include a description of the following items by treatment arm:

- Number of participants enrolled and randomized
- Number of participants included in each population
- Number and percentage of participants who prematurely withdrew from the study or from study treatment (including the reasons for discontinuation and the distribution of these discontinuations by time-windowed visit)
- Incidence of protocol deviations – overall and by four main categories (inclusion criteria, exclusion criteria, medication and procedural)
- Stratification factor reported in IxRS and used for randomization vs. stratification factor reported in the eCRF
- Number of participants with home nursing
- Number of participants initiating or changing symptomatic treatment of AD during the study

Major protocol deviations and premature withdrawals will be listed.

5.7.2 Summaries of Treatment Group Comparability

Demographics and baseline characteristics (including age, sex, medical history, randomization stratification factors) will be summarized descriptively by treatment arm as assigned for the ITT population using:

- means, SDs, medians, and ranges for continuous variables
- counts and proportions for categorical variables

Exposure to AD concomitant medication (including post-baseline initiation or change in dose) will be summarized by treatment arm for the ITT population.

Participants are eligible for study participation whether or not they are receiving approved medication for AD (i.e., acetylcholinesterase inhibitors, memantine, and/or medical food supplements, where approved) with the exception of GV-971.

5.7.3 Summaries of COVID-19 Impact on the Trials

Studies WN29922 and WN39658 were ongoing during the COVID-19 pandemic. Consequently, to monitor the potential impact of the pandemic on the trials, we will provide a specific set of descriptive analyses related to COVID-19, including:

- COVID-19 AEs (see Section 5.6.2)
- COVID-19 related Protocol Deviations
- Missed doses due to COVID-19
- Study discontinuations due to COVID-19
- Missed outcome assessments due to COVID-19
- Study drug administrations of 1020 mg Q4W
- Remote scale administrations
- Site actions and site closures
- Frequency of change in caregiver and rate with calendar time

5.7.4 Immunogenicity Analyses

Immunogenicity analyses include the evaluation for antibodies against gantenerumab, including the determination of antibody titers. The results of the confirmatory assay will be presented as a frequency table summarizing baseline and post-baseline results.

A listing of participants with positive ADA status per confirmatory assay and titer result will be provided.

5.7.5 Analyses of Subgroups of Interest

5.7.5.1 Tau PET Substudy

There is a single tau PET substudy enrolling subjects from both studies (WN29922/WN39658 Longitudinal Tau PET Substudy). This substudy utlilizes [^{18}F]GTP1 (RO6880276) as tau PET radioligand.

Exploratory analyses will be conducted on tau PET Standardized Uptake Value Ratios (SUVR) in the following four target regions of interest. In composite target regions, each region is weighted by its own volume.

- A temporal composite target region. This region is composed of (both left and right):
    - anterior and posterior superior temporal gyrus,
    - posterior temporal lobe,

- fusiform gyrus,
- middle and inferior temporal gyrus;

- A medial temporal composite region not including the hippocampus, composed of (both left and right):
  - Amygdala,
  - Parahippocampus,
  - Anterior medial and lateral temporal lobe;
- Frontal lobe (both left and right);
- Parietal lobe (both left and right);

The inferior cerebellar grey matter will be used as reference region for the calculation of SUVRs for all four target regions considered.

Analysis Approach

An MMRM analysis adjusting for baseline tau PET SUVR, and APOE ε4 status (carrier vs. non-carrier) will be used to estimate the mean change from baseline to Week 116 for each of the SUVRs defined above. The model will include the change from baseline in SUVR as the dependent variable. The effects in the model will also include treatment group, visit, APOE ε4 status, baseline SUVR, baseline SUVR-by-visit and treatment-by-visit interaction. Visit will be treated as the repeated variable within a participant. APOE ε4 status, participant, treatment, and visit week will be treated as class variables. An unstructured variance covariance matrix will be applied to model the within-participant errors; in the case of non-convergence, compound symmetry will be used.

5.7.5.2 Biomarker Analyses

Biomarker data will be summarized by treatment group for each assessment visit using descriptive statistics of absolute values as well as change from baseline values. Plasma and CSF biomarkers will be analysed using MMRM models after log transformation. The following pharmacodynamic biomarkers will be analysed:

- Cerebrospinal Fluid (CSF):
  - Total tau (tTau)
  - Phosphorylated tau (pTau)
  - Neurogranin
  - Neurofilament (NFL)

- Plasma:
    - Phosphorylated tau (pTau)
    - Neurofilament (NFL)
- MRI-derived measurements, including:
    - Volumetric changes in whole brain, ventricles, hippocampus, cortical gray or other structures

In addition, other exploratory biomarkers will be reported separately.

5.8 INTERIM ANALYSES

Details of interim analysis plans are described in a separate interim analysis SAP (iSAP), providing information about:

- a futility interim analysis based on the primary efficacy endpoint CDR-SOB
- an amyloid PET interim analysis based on the change in Amyloid PET Centiloids
- If results from the amyloid PET interim analysis met the pre-specified criteria as described in the iSAP and the amyloid PET substudy results are presented to health authorities, they will be supplemented by high-level summaries of safety (at an aggregated level for each arm) from the overall parent phase-3 study population. An external and independent statistical group will perform these potential additional safety analyses in order to preserve the blinding and the overall integrity of the parent studies. In any case, the studies will continue unchanged until its planned completion.

Other than the futility analysis, there is no plan for an efficacy interim analysis based on the primary endpoint. The primary analysis of the clinical efficacy endpoints will be performed only once, after completion of the efficacy data collection at the end of the double blind part of the study (as described in this SAP) and it will be the only opportunity to formally reject the primary null hypothesis of the trial. Thus, a multiple testing adjustment procedure will not be necessary to control the overall Type I error rate for the primary (CDR-SOB) and secondary endpoint efficacy analyses as a result of this interim analysis and will therefore not be applied.

6. SUPPORTING DOCUMENTATION

This document is part of a broader Data Analysis Plan that has several documents, including:

- Graduates studies interim analysis SAP
- Graduate amyloid PET substudy SAP
- Graduates studies Data Analysis Plan Module 2
- Graduates studies Data Analysis Plan Module 3

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Appendix 1 Proof of Equivalence Between Conditional Mean Imputation and a Large Number of Random Imputations

The proposed treatment effect estimator differs from the conventionally used implementation of reference based imputation methods (Carpenter et al, 2013 and Cro et al, 2020) in two ways. First, the imputation is based on REML estimation of the parameters from the imputation model rather than on Bayesian posterior draws. As demonstrated in von Hippel and Bartlett 2020 and Wang and Robins 1998, imputations based on ML parameter estimation are more efficient, have less small–sample bias, and avoid the complexities of Bayesian model fitting, which would require the specification of prior distributions and Markov chain Monte Carlo (MCMC) computational methods.

Second, the treatment effect estimator from Section 5.3.3 is based on an ANCOVA model applied to a single deterministic imputed dataset set using conditional mean imputation whereas conventional approaches require multiple randomly imputed datasets. As demonstrated below, an analysis of completed data based on deterministic conditional mean imputation results in the same treatment effect estimate as would be obtained via pooling of treatment effects estimates across an infinite number of randomly imputed datasets. Therefore, conditional mean imputation does not lead to any bias but rather provides a convenient shortcut to generating a large number of random imputations. It also does not artificially decrease variance, because variance estimation will be based on resampling techniques (as described in Section 5.3.3) and not on the (naïve) standard error of the treatment effect estimate from the single imputed dataset.

Denote the treatment effect estimate from an ANCOVA model applied to the single imputed dataset via conditional mean imputation by $\hat{\theta}_{CMI}$. Alternatively, von Hippel and Bartlett (2020) proposed to perform *M* random imputations, analyze each of these *m* imputed datasets via an ANCOVA model separately leading to *m* treatment effect estimators $\hat{\theta}_{SI,m}$, and then use their average as the overall treatment effect estimate, $\hat{\theta}_{SI,M}$.

$\hat{\theta}_{SI,M} \coloneqq \frac{1}{M}\sum_{m=1}^{M}\hat{\theta}_{SI,m}$. It is easy to demonstrate that the two approaches are closely connected and that both overall treatment estimates converge almost surely as *M* increases.

$\hat{\theta}_{SI,M} \rightarrow \hat{\theta}_{CMI}$ as $M \rightarrow \infty$ (almost surely)

To prove this, let Y_m and Y_{CMI} correspond to the imputed outcome vector from the visit relevant to the primary endpoint for all participants based on the *m*th randomly imputed dataset and the conditional mean imputation, respectively. Then $\frac{1}{M}\sum_{m=1}^{M} Y_m \rightarrow Y_{CMI}\ as\ M \rightarrow \infty$ (almost surely) by the strong law of large numbers (because Y_m is equal to $Y_{CMI} + mean\ 0\ noise$). Let X denote the design matrix of the ANCOVA analysis model (which is identical for all multiply imputed datasets). Denote the vector of estimated

regression coefficients from the ANCOVA model by $\hat{\beta}_{SI,m}$ and $\hat{\beta}_{CMI}$ for the *m*th randomly imputed dataset and the conditional mean imputed dataset, respectively. Then

$$\widehat{\beta}_{SI,M} \coloneqq \frac{1}{M}\sum_{m=1}^{M}\hat{\beta}_{SI,m} = \frac{1}{M}\sum_{m=1}^{M}(X^tX)^{-1}X^tY_m = (X^tX)^{-1}X^t\sum_{m=1}^{M}\frac{1}{M}Y_m \rightarrow (X^tX)^{-1}X^tY_{CMI} = \hat{\beta}_{CMI}$$

as $M \rightarrow \infty$ (almost surely), X^t denotes the transpose of X and $(X^tX)^{-1}$ denotes the inverse of X^tX.

This proves the statement because $\hat{\theta}_{SI,M}$ and $\hat{\theta}_{CMI}$ correspond to one element from the regression coefficient vectors $\hat{\beta}_{SI,M}$ and $\hat{\beta}_{CMI}$, respectively.

Appendix 2 Other Intercurrent Events of Potential Scientific Interest

Table A.2. Other Intercurrent Events of potential scientific interest

Intercurrent Event	SDCR/NSDCR	Estimand Approach
Starting another treatment for AD	SDCR	Treatment Policy
Changing the dose of a symptomatic treatment for AD	SDCR	Treatment Policy
Treatment interruption (any duration) due to ARIA-E	SDCR	Treatment Policy
Nursing home placement	SDCR	Treatment Policy
Significant reduction in drug exposure due to the COVID-19 pandemic site closure (defined as ≥ 16 weeks)	NSDCR	Hypothetical Strategy

AD = Alzheimer's disease; ARIA-E = amyloid-related imaging abnormalities – edema/effusion; COVID-19 = coronavirus 2019; NSDCR = Non Study Drug or Condition Related; SDCR = Study Drug or Condition Related.

Appendix 3 Charter for Adjudication Committee for Intercurrent Events

CHARTER FOR ADJUDICATION COMMITTEE FOR INTERCURRENT EVENTS

TITLE:	**TWO PHASE III, MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY, AND SAFETY STUDIES OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**
PROTOCOLS:	WN29922, WN39658
AUTHOR:	[redacted]
IND NUMBERS:	102,266
EUDRACT NUMBERS:	2017-001364-38 (Study WN29922) 2017-001365-24 (Study WN39658)
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	01 September 2021

TABLE OF CONTENTS

1. VERSION HISTORY

Version	Date	Details
Version 1	01September2021	Creation

ADJUDICATION COMMITTEE FOR INTERCURRENT EVENTS MEMBER SIGNATURES

TITLE: **TWO PHASE III, MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY, AND SAFETY STUDIES OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**

PROTOCOLS: WN29922
WN39658

I have read this Charter and confirm that, to the best of my knowledge, it accurately describes the conduct of the Adjudication Committee for Intercurrent Events.

DocuSigned by:
[redacted]
B97097216CF14A1...

[redacted], MD
[redacted],
F. Hoffmann-La Roche Ltd
(ACI [redacted])

Date 9/1/2021

ADJUDICATION COMMITTEE FOR INTERCURRENT EVENTS MEMBER SIGNATURES

TITLE: **TWO PHASE III, MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY, AND SAFETY STUDIES OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**

PROTOCOLS: WN29922
WN39658

I have read this Charter and confirm that, to the best of my knowledge, it accurately describes the conduct of the Adjudication Committee for Intercurrent Events.

DocuSigned by:
[redacted]
C73603349D0D4C4...

[redacted]
F. Hoffmann-La Roche Ltd

Date 9/2/2021

ADJUDICATION COMMITTEE FOR INTERCURRENT EVENTS MEMBER SIGNATURES

TITLE: **TWO PHASE III, MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY, AND SAFETY STUDIES OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**

PROTOCOLS: WN29922
WN39658

I have read this Charter and confirm that, to the best of my knowledge, it accurately describes the conduct of the Adjudication Committee for Intercurrent Events.

DocuSigned by:
[redacted]
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[redacted]
F. Hoffmann-La Roche Ltd

Date 9/2/2021

2. INTRODUCTION

RO4909832 (gantenerumab) is a fully human monoclonal antibody targeting aggregated forms of amyloid-β including oligomers, fibrils, and plaques. Studies WN29922 and WN39658, defined as GRADUATE studies, will evaluate the efficacy and safety of gantenerumab compared with placebo for the treatment of patients with early (prodromal to mild) Alzheimer's disease.

Intercurrent events (ICEs) are defined as events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. In order to estimate precisely the treatment effect as described as the primary estimand, it is crucial to correctly identify and address these ICEs. ICEs will either be considered Non Study Drug or Condition Related (NSDCR) or Study Drug or Condition Related (SDCR). For the primary estimand of the GRADUATE studies, the Sponsor is proposing a treatment policy approach for all SDCR ICEs. All remaining NSDCR ICEs will be handled using a hypothetical approach.

This Charter contains a description of the adjudication committee for intercurrent events (ACI) membership and operations for Studies WN29922 and WN39658. The ACI will review the ICEs related to study treatment discontinuation where ambiguity exists in order to support the study team classifying them as NSDCR or SDCR as per the SAP.

Terms and abbreviations used in this Charter are defined in Table 1.

Table 1 Terms and Abbreviations

Term and Abbreviation	Definition
ACI	Adjudication committee for intercurrent events
eCRF	electronic Case Report Form
ICEs	Intercurrent events
NSDCR	Non Study Drug or Condition Related
SDCR	Study Drug or Condition Related
Sponsor	F. Hoffmann-La Roche Ltd
Study Team	Team composed of Sponsor employees directly involved with the study leadership team (SLT)
unblinding data	data for which treatment assignment is identified

3. ROLE OF THE COMMITTEE

The Study Team delegates to the ACI the responsibility to review and sort ICEs as SDCR or NSDCR according to prespecified ICE categories defined in the study SAP for those cases of study treatment discontinuation where reasons are not precisely captured by the eCRF. These cases will be identified by the GRADUATE Study Team after completion of data cleaning efforts

including medical data review. The predefined ICE categories are the following (specific ICEs may be added to the list if deemed necessary by the ACI):

Table 2 ICE Categories

Intercurrent Event (ICE)	SDCR/NSDCR
Withdrawal from study treatment due to lack of efficacy	SDCR
Withdrawal from study treatment due to safety or tolerability reason (NOTE: This will include discontinuations due to AE, incl. suspected or confirmed COVID-19 AEs)	SDCR
Withdrawal from study treatment with no informative reason given	SDCR
Withdrawal from study treatment due to the COVID-19 pandemic	NSDCR
Significant reduction in drug exposure due to the COVID-19 pandemic (defined as ≥ 4 missed dose-months)	NSDCR
Withdrawal from study treatment due to purely administrative reason	NSDCR
Death	NSDCR
Withdrawal from study treatment due to use or initiation of protocol prohibited medication	SDCR
Withdrawal from study treatment due to other SDCR ICEs	SDCR

The ACI will review discontinuation cases where the reason for study treatment discontinuation and substudy discontinuation is non informative and captured in the eCRF as 'Protocol deviation', 'Withdrawal by subject', 'Physician decision' or 'Other'. For these cases, free text is captured in the eCRF.

The ACI will review data provided by the GRADUATE Study Team (described in section 4.2). By carefully reviewing data relative to the ICEs, the ACI will help the GRADUATE Study Team achieve an objective classification of ICEs as SDCR or NSDCR.

4. COMMITTEE MEMBERSHIP

4.1 MEMBERS

The ACI is composed of a chair and two additional members. The Chair has the responsibility to digitally sign the ICEs Categorization Report and the form documenting that a meeting of the ACI took place.

Members: [redacted], MD
[redacted],
F. Hoffmann-La Roche Ltd
(ACI [redacted])

[redacted]
F. Hoffmann-La Roche Ltd

[redacted]
F. Hoffmann-La Roche Ltd

4.2 ACI MEMBERS SELECTION CRITERIA

The ACI members may be employees of the Sponsor or any contract research organization that works with the Sponsor. The committee should include three members representing at least one of the following line functions: Clinical Science, Data Science, and Safety Science. ACI members should not have been involved in the conduct of Studies WN29922, WN39658, and related substudies, should not have been exposed to unblinding data of the studies in scope, and should have a minimum of two-years experience in clinical trials conduct. Based on the aforementioned criteria, ACI members will be selected by the GRADUATE Study Team.

Members of the ACI who do not fulfill all the selection criteria and whose ACI membership may materially affect objectivity will be asked to resign from the committee and will be replaced.

4.3 DURATION OF THE ACI MEMBERSHIP

The membership will extend for the duration of the Studies in scope (see Section 1), at least up to the time the database for primary analysis is locked and the study is unblinded to the Sponsor. If a member leaves the ACI, the GRADUATE Study Team will select a replacement based on the criteria described in section 3.2.

5. COMMITTEE MEETINGS

5.1 ORGANIZATIONAL MEETING

A first introduction meeting will formally establish the ACI and acquaint the ACI with the process that will be followed. In advance of the organizational meeting the committee will have received the study protocols, the IBs, the blank eCRF and the SAP (the latest draft if not yet final).

5.2 SCHEDULED MEETINGS

The number of meetings will depend on the amount of data to be reviewed by the ACI. The Study Team and the ACI will agree on the number of meetings to be held during the organizational meeting.

The Study Team will prepare reports including data to be reviewed. These reports will be provided to the ACI at least three business days prior to each meeting (Appendix 1). The content of these reports is limited to eCRF data extracted from:

- "Study Drug Completion/Early Discontinuation" form including :
  - "Completion/discontinuation reason" item
  - Free text field " If primary reason is protocol deviation, withdrawal by subject, physician decision or other, specify"

The data will be extracted from the eCRF and provided in a tabular format to the committee. ACI meetings will not be attended by the GRADUATE Study Team.
For ACI meetings to take place all three members should be attending. The decisions should be made in a unanimous way. However if this is not possible in some cases, the Chair has the casting vote.

6. COMMUNICATION AND DATA FLOW

6.1 COMMUNICATION

The GRADUATE study team will communicate to the ACI the meeting dates and the SPA responsible will extract data to be reviewed. The ACI will communicate the adjudicated ICEs to the GRADUATE Study Team and the SPA responsible (see section 5.2).

ACI members are to treat all communications regarding these clinical studies, including reports, data, review meeting discussions, teleconferences, and meeting minutes, as confidential material.

All communications relative to these meetings will be archived in the eTMF.

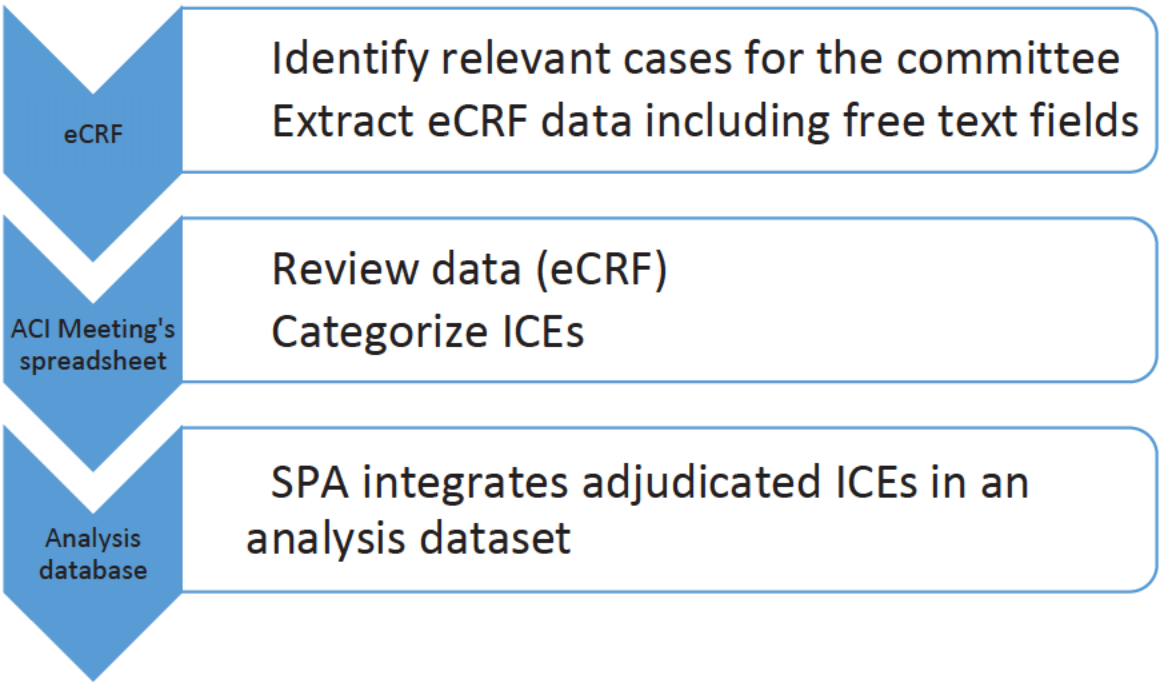
6.2 ICEs CATEGORIZATION REPORT

After each scheduled meeting, ACI will provide input on ICEs categorization during the meetings to the GRADUATE Study Team within seven business days. The format of ICEs Categorization Report will be in a tabular format. An example is presented in Appendix 2.

The GRADUATE Study Team will collect the outcome of ACI meetings, integrate them in an analysis dataset, and archive the documents in the eTMF.

7. APPENDIX 1

Organization flowchart



8. APPENDIX 2

The format of ICEs Categorization Report

Treatment discontinuation reason	Reason specification	ICE Categorization
Protocol deviation / Withdrawal by subject / Physician decision / Other	<eCRF free text>	Withdrawal from study treatment due to lack of efficacy / Withdrawal from study treatment due to safety or tolerability reason / etc.
etc.		

STATISTICAL ANALYSIS PLAN

STUDY TITLE: **TWO PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP EFFICACY AND SAFETY STUDIES OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**

STUDY NUMBER: WN29922, WN39658

STUDY NAME: GRADUATE I, GRADUATE II

VERSION NUMBER: 2.0

ROCHE COMPOUND(S): Gantenerumab (RO4909832)

EUDRACT NUMBER: 2017-001364-38 (WN29922)
2017-001365-24 (WN39658)

IND NUMBER: 102,266

NCT NUMBER: NCT03444870

PLAN PREPARED BY: [redacted], [redacted], [redacted]

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

SPONSOR: F. Hoffmann-La Roche Ltd
LEGAL REGISTERED ADDRESS: Grenzacherstrasse 124
4070 Basel, Switzerland

DATE FINAL: See electronic date stamp on the last page of this document

STATISTICAL ANALYSIS PLAN VERSION HISTORY

This SAP was developed based on Roche SAP model document v2.0, revised 26 October 2020.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
2	see electronic date stamp on last page of the document	Version 5.0, 2 August 2021
1	12 October 2021	Version 5.0, 2 August 2021

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Key changes to the SAP version 1.0, along with the rationale(s) for each change, are summarized below.

Section	Description of Change	Rationale for Change
Section 1	It has been clarified that the OLE part will also be reported (safety only)	To add clarity.
Section 1.1	Change from baseline to Week 116 in amyloid PET has been added among the list of pharmacodynamics biomarkers.	Following the decision to not pursue an interim analysis for amyloid PET, the planned analyses have been added to this document.
Section 4	The definitions of the CSF modified ITT has been relaxed to only require at least one valid CSF measurement instead of requiring at least one 'post-baseline' CSF measurement, without anymore mentioning specific biomarkers.	In order to include as many participants as possible.
Section 4	The definitions of the Amyloid PET modified ITT and Tau PET modified ITT analyses sets have been simplified.	To add clarity.
Section 4	New 'longitudinal' analyses sets have been added for all the biomarkers (amyloid-PET-longitudinal, Tau-PET-longitudinal, CSF-longitudinal, Plasma-longitudinal and MRI-longitudinal), requiring at least one valid post-baseline measurement.	This new analyses set will be more representative of the patients that will contribute to the considered statistical model.
Section 4	New analyses sets, Amyloid-PET Safety evaluable and Tau-PET Safety Evaluable, have been added.	The safety outputs for the amyloid-PET and Tau-Pet sub-studies will be based on those analyses sets.
Section 5.1	A definition of the clinical cutoff for the primary analysis has been added.	To add clarity
Section 5.1	More details have been provided to the baseline definition.	To add clarity.
Section 5.1	For CSF and plasma biomarkers, it has been clarified how to deal with values below the lower limit of quantification and above the upper limit of quantification.	To add clarity.
Section 5.3.1	More details have been added to the description of the primary endpoint.	To add clarity

Section 5.3.2	For the primary estimand, the 'treatment' attribute has been slightly modified.	It now explicitly includes safety-related dose modification as part of the intended treatment.
Section 5.3.2	In the ICE Derivation paragraph, the algorithm on how to derive the number of missed dose-months has been described.	To add clarity.
Section 5.3.3	A time windowing for clinical endpoints has been added.	In response to FDA feedback on 2 May 2022. To add clarity.
Section 5.3.3	In the analysis step of the main analytical approach for primary estimand and primary endpoint, it has been clarified that analysis at visits other than Week 116 will be reported as supplementary analyses. In addition, it has been specified that the treatment effect will be reported as a difference in adjusted means and also as a relative difference (for descriptive purposes).	Clarify that the primary analysis relies on the estimation of treatment effect at a single time point, which is Week 116.
Section 5.3.3	In the 'description of the primary estimator', the link to a published manuscript, providing more detailed justification of the statistical methodology for the primary estimator and supportive simulations, has been added	Publication now available.
Section 5.3.3	In the 'Analysis step' for the description of the primary estimator, a definition of 'AD medication at baseline' has now been provided.	To add clarity.
Section 5.3.3.1	A reference to a published manuscript describing the R's rbmi package has been added.	Publication now available.
Section 5.3.4	The MMRM paragraph has been moved from the 'Sensitivity Analyses' section into the 'Supplementary Analyses' section.	Given that it is not targeting the primary estimand.
Section 5.3.5.1	The definition of certain subgroup analyses for the primary endpoint has been updated: - age groups have now been defined based on a median split - it has been clarified that geographic region will be based on IXRS - for baseline disease severity: the subgroups defined by MMSE and CDR-	There was no strong rationale to derive age groups based on the threshold of 65 years. The subgroup analysis for disease stage has been simplified, given that there are already two additional criteria: one based on the physician judgment and the other based on the CDR-GS.

	GS baseline measures have been removed 'MMSE≥ 24 and CDR-GS = 0.5' vs 'MMSE < 24 or CDR-GS > 0.5' - Use of symptomatic AD medication: it has been clarified that this will be based on any use of the following 4 medications: donepezil, galantamine, memantine and rivastigmine.	In addition, defining disease stage by a combination of MMSE and CDR-GS is not a standard clinical approach.
Section 5.3.5.2	The paragraph describing the 'treatment policy estimand' has been modified, by adding more details.	To add clarity.
Section 5.3.5.2	A primary threshold of interest has been added for the progressor analysis on the CDR-SB, including a reference. In addition more details of the analyses have been provided.	Better pre-specification of the progressor analysis.
Section 5.3.5.2	Addition of a sub-section: "Treatment effect estimate before week 116"	Clarify that the Sponsor is planning to estimate the treatment effect on the CDR-SB at other timepoints than Week 116.
Section 5.3.5.2	A new MMRM paragraph has been added (it has been moved from the sensitivity analyses section). It now uses all the available data independently of the occurrence of any ICE. Additionally it has been specified that in case of non-convergence with the unstructured covariance structure, then compound symmetry will be used, together with a robust estimator of standard error.	This analysis aims to provide a reference point analysis method described in early versions of the protocol (up to version 4) and to other external analyses where MMRM was considered the default and primary analysis. Addition of a robust estimator of standard error, in case of no convergence, it is to protect type-I error in case of an under-specification of the true covariance matrix.
Section 5.3.5.2	Addition of a new paragraph: "Impact of ARIA-E MRI finding on the primary outcome"	Additional analysis to assess the potential influence of ARIA-E on the primary outcome.
Section 5.4	The covariates, to be considered for the ANCOVA analyses of the secondary clinical endpoints, have been specified. In addition, it has been specified that analyses at visits other than week 116 will be reported as supplementary analyses	To add clarity.

Section 5.4.1	A supportive MMRM analysis for confirmatory secondary endpoints has been added.	Additional supportive analyses.
Section 5.5	It has been clarified that for exploratory ordinal endpoints only descriptive analyses will be considered.	Before there was no description on how to analyze ordinal endpoints
Section 5.5	TheEuroQoL–5 Dimensions visual analog scale (EQ-5D VAS) has been removed from the list of exploratory endpoints	Study team decided to report this endpoint, used in health economic analyzes, in a separate document
5.5.1.9	The section describing the Resource Utilization in Dementia Scale Lite (RUD-Lite) has been removed.	Study team decided to report this endpoint, used in health economic analyzes, in a separate document
5.5.1.10	The section describing EuroQoL–5 Dimensions visual analog scale (EQ-5D VAS) has been removed.	Study team decided to report this endpoint, used in health economic analyzes, in a separate document
Section 5.6	More details have been added to specify when safety data will be reported in the double-blinded treatment period, the follow-up period or the OLE period.	To add clarity.
Section 5.6.2	It was clarified that the summary tables of AEs will be restricted to treatment-emergent AEs, i.e., AEs that occur on or after the day of first dose of study drug.	To add clarity.
Section 5.6.2	Hypersensitivity reactions have been added among the safety information to be summarized.	To align with the overall safety strategy in the Gantenerumab program.
Section 5.6.3	It was clarified that not all ARIA MRI findings qualify as AE. ARIA analyses will be mainly based on ARIA MRI findings. ARIA AEs will also be reported.	To add clarity.
Section 5.6.3	The analysis of ARIA-H by APOE ε4 genotype will be based on the number of alleles rather than carrier vs non-carrier	To align with the overall safety strategy in the Gantenerumab program.
Section 5.7.5	An entire new section has been added to describe the planned analyses for the Amyloid PET substudies.	Following the decision to not pursue an interim analysis for amyloid PET, the planned analyses have been added to this document.
Section 5.7.6	An estimand has been defined to describe the analyses for the Tau PET outcome measures.	Clarify the analysis plan for the Tau-PET substudy.

Section 5.7.6	It has been made clear that the Tau PET measure of interest is the median SUVR rather than SUVR .	To add clarity
Section 5.7.6.1	A new section 'Summaries of Treatment Group Comparability' has been added.	For completeness.
Section 5.7.6.3	More details related to the main estimator have been added.	To make it consistent with the corresponding estimand
Section 5.7.6.3	It has been added that the change from baseline to Week 52 in tau PET will also be reported as supplementary analysis.	Additional supportive evidence
Section 5.7.6.4	A time windowing for tau PET assessments has been added.	To add clarity.
Section 5.7.7 to Section 5.7.9	The sections on the CSF biomarkers, plasma biomarkers and Volumetric MRI biomarkers have been updated by adding more details of the statistical analyses.	Clarify analysis plan for each type of biomarker
Section 5.8	The wording on the interim analysis for the amyloid PET has been removed.	The sponsor decided not to conduct an interim analysis on amyloid PET in the amyloid PET substudy
Appendix 1	Appendix 1 has been changed (before it contained details about the methodology of the primary estimator) to focus on general considerations and simulations related to type-I error	This is because a published manuscript (Wolbers et al. 2021) has now become available, describing in details the methodology of the primary estimator. The new focus on type-I error was in response to FDA feedback on May 2nd 2022.
Section 5.5.1.2, Appendix 2	A new appendix has been added describing the algorithm used to derive the ADCS-ADL Dependence Scale.	Provide details on the derivation of the ADCS-ADL dependency score

Additional minor changes have been made throughout the document to improve clarity and consistency.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
Aβ	amyloid-beta
AD	Alzheimer's disease
ADA	anti-drug antibody
ADAS-Cog11 / Cog13	Alzheimer disease assessment scale – cognition, subscale 11 / 13
ADCS-ADL	Alzheimer disease cooperative study - activities of daily living
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
APOE	apolipoprotein ε
ARIA-E	amyloid-related imaging abnormalities – edema/effusion
ARIA-H	amyloid-related imaging abnormalities – hemosiderin deposition
CDR-GS	clinical dementia rating – global score
CDR-SB	clinical dementia rating – sum of boxes
CIR	copy increments from reference
CNS	central nervous system
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
CSR	Clinical Study Report
C-SSRS	Columbia-suicide severity rating scale
DTI	diffusion tensor imaging
ECG	Electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EQ-5D	EuroQol-Five Dimensions
FAQ	functional activities questionnaire
FDA	(U.S.) Food and Drug Administration
ICE	intercurrent event
ICH	International Council on Harmonization
iDMC	independent Data Monitoring Committee
IRC	independent review charter

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS (Cont'd)

Abbreviation or Term	Description
ISR	injection-site reaction
ITT	intent to treat
IxRS	interactive voice/web-based response system
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MMRM	mixed effects model repeated measures
MMSE	mini-mental state examination
MNAR	Missing not at random
MRI	magnetic resonance imaging
NMPA	National Medical Products Administration
NPI-Q	neuropsychiatric inventory-questionnaire
NSDCR	not study drug or condition related
OLE	open-label extension
PET	Positron emission tomography
PK	Pharmacokinetic
pTau	phosphorylated tau
Q2W	every 2 weeks
Q4W	every 4 weeks
QoL	quality of life
QoL-AD	quality of life – Alzheimer's disease
RUD-Lite	resource utilization in dementia - lite
SAE	serious adverse events
SAP	Statistical Analysis Plan
SC	Subcutaneous
SDCR	study drug or condition related
SUV	standard uptake value
SUVR	standard uptake value ratio
tTau	total tau
ZCI-AD	Zarit caregiver interview – Alzheimer's disease

1. INTRODUCTION

This document describes the statistical analyses that will be reported in the primary Clinical Study Reports (CSR) of Studies WN29922 (hereafter referred to as "GRADUATE I") and WN39658 (hereafter referred to as "GRADUATE II"). The descriptions, methodology, and analyses presented in this document applies to both studies unless otherwise specified. The efficacy estimands and safety endpoints that will be the basis for comparing the two treatment arms will be defined in full in this document along with the populations of participants that are to be used in the analyses.

This Statistical Analysis Plan (SAP) covers analyses planned for the double-blind treatment period and the safety follow-up across both studies. Analyses for the OLE phase will focus on safety and will be listed directly in the corresponding List of Planned Outputs (LoPO). Pharmacokinetic (PK) data will be reported in a separate population PK report and thus is not covered in this document. Similarly, health economic data (such as utility values derived from the EQ-5D-5L and the RUD-lite) will be analyzed and reported separately from the Clinical Study Report and are therefore not covered in this document.

The description of layouts for the CSR outputs, the details about the underlying analysis datasets and programs, and the linking of production outputs to sections in the CSR are not within the scope of this document and will be covered in separate documents, i.e., Data Analysis Plan Module 2 and 3.

The language used in this SAP supersedes that in the protocol and protocol synopsis.

An early draft of this SAP was presented to U.S. Food and Drug Administration (FDA) in the context of a Type C meeting (Written Response Only procedure, December 21, 2020, Ref ID: 4720726) and to the European Medicines Agency (EMA) in the context of Scientific Advice procedure (EMA Written Advice received on 29 January 2020; EMA//SA/0000046418). These procedures focused on the proposed primary estimand, the estimator and other aspects of the analysis plan. Both agencies in principle agreed on the primary question of interest in the context of the estimand framework (ICH E9[R1]). There was also agreement on the proposed hierarchy of secondary endpoints.

A more advanced version of the SAP was submitted to the FDA for their review in December 2021. The feedback received during these health authority interactions was duly considered and informed the current version of this SAP.

1.1 OBJECTIVES

This study will evaluate the efficacy and safety of gantenerumab compared with placebo in participants with early (prodromal to mild) AD.

Table 1 Objectives and Corresponding Endpoints

Primary Objective(s)	Corresponding Endpoint(s)
• To evaluate the efficacy of gantenerumab administered by SC injection compared with placebo	• The change in global outcome from baseline (Day 1) to Week 116, as measured by the CDR-SB
Secondary Objective(s)	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo on cognition and/or function	The change from baseline to Week 116 in cognition and/or function, as measured by: • MMSE total score • ADAS-Cog11 and ADAS-Cog13 • Verbal Fluency Task • Coding • FAQ • ADCS-ADL total score and instrumental score
Exploratory Objective(s)	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo	The change from baseline to Week 116 in the following: • Clinically evident decline as measured using the CDR • Severity, as assessed by the CDR Global Score • Dependence level, as derived from the ADCS-ADL score • Health-related quality of life, as assessed by the QoL-AD scale • Behavioral and neuropsychiatric symptoms of AD, as measured by the NPI-Q • Study partner burden, as assessed by the ZCI-AD scale • Elements of resource utilization, as assessed by the RUD-Lite • Health outcomes in participant and study partner, as measured by EQ-5D questionnaire

Table 1 Objectives and Corresponding Endpoints (cont.)

Safety Objective(s)	Corresponding Endpoints
• To evaluate the safety of gantenerumab compared with placebo	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Presence of ADAs during the study relative to the presence of ADAs at baseline (in active drug group only)
Pharmacodynamic Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo	• Change from baseline to Week 116 in brain amyloid load, as measured by amyloid PET scan in a subset of participants • Change from baseline to Week 116 in brain tau load, as measured by tau PET scan in a subset of participants • Change from baseline to Week 116 in cerebrospinal fluid markers of disease in a subset of participants, including, but not limited to total tau, and phosphorylated tau
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo	• Change over time in plasma and other CSF biomarkers • Change from baseline to Week 116 in functional brain connectivity, as measured by resting-state functional MRI (where available) • Change from baseline to Week 116 in integrity of white matter, as measured by DTI-MRI (where available) • Change in MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all participants

AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale-Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale-Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group-Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities-edema/effusion; ARIA-H = amyloid-related imaging abnormalities-hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SB = Clinical Dementia Rating-Sum of Boxes; CSF = cerebrospinal fluid; C-SSRS = Columbia-Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory-Questionnaire; PET = positron emission tomography; QoL-AD = Quality of Life-Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia-Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview-Alzheimer's Disease.

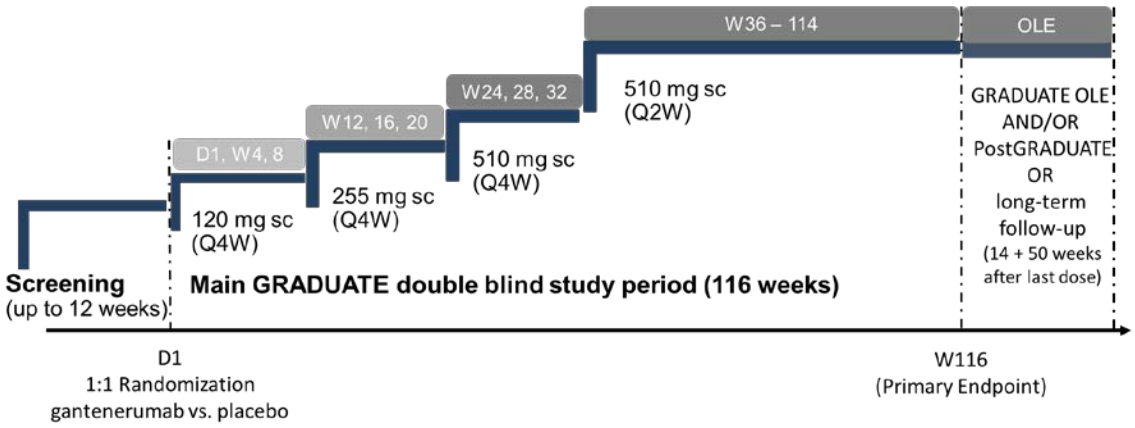
1.2 STUDY DESIGN

GRADUATE I and GRADUATE II are two identical Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies designed to evaluate the efficacy and safety of gantenerumab in participants with early (prodromal to mild) AD.

The planned number of participants for the global enrollment phase for each study is approximately 1016 participants randomized in a 1:1 ratio to receive active drug or placebo (508 participants randomized to active drug and 508 randomized to placebo; see Section 3). To maintain a balanced number of participants enrolled in each treatment arm and to ensure that the arms are comparable, randomization will be stratified by stage of the disease (prodromal AD vs. mild AD), apolipoprotein ε4 (APOE) allele status (presence vs. absence of the ε4 allele), use of AD medication (presence vs. absence), geographic region (Western Europe and Australia vs. Rest of the World vs. North America), and participation in the longitudinal amyloid and tau PET substudies. Approximately 175 centers in approximately 15 countries worldwide will participate in these studies.

Due to the global impact of the coronavirus disease (COVID-19) pandemic and the resulting disruption in study drug administration, the duration of the double-blind treatment period was extended by 12 weeks, with Protocol Amendment 4. The optional scenario of a further extension of 12 weeks – resulting in a final efficacy and safety visit at Week 128 – was not implemented. An overview of the study design is provided in Figure 1.

Figure 1 Overall Study Design



Each study consists of three distinct periods:

Screening (including an optional prescreening): The screening period may last up to 12 weeks for each eligible participant.

Double-blind treatment period: After screening, participants who meet all eligibility criteria will be randomly assigned to one of two arms (active drug or placebo) in a 1:1 ratio. Following baseline assessments, each participant will receive a minimum of 9 subcutaneous (SC) administrations every 4 weeks (Q4W) of study drug (uptitration period), followed by up to 40 administrations every 2 weeks (Q2W) of study drug at target dose in the double-blind treatment period. The last dose of study drug will be administered at Week 114. At the end of the double-blind treatment period, 2 weeks after the last dose, all participants will undergo the final efficacy and safety study visit. Participants who have already completed the double-blind treatment period prior to implementation of Protocol Version 4 will have received up to 34 SC Q2W administrations of study drug during the double-blind treatment period. The last dose will have been administered at Week 102, and their final efficacy and safety visit will be at Week 104.

The Sponsor will emphasize to Investigators the importance of collecting data for the primary endpoint through Week 116, even if participants withdraw from treatment but do not withdraw from the study.

Post-double-blind treatment period: After the final efficacy and safety study visit for the double-blind treatment period, all participants will be asked to come back for the long-term follow-up visits or to continue in the open-label extension (OLE). Participants will either directly enter the separate WN42171 (hereafter referred to as "POSTGRADUATE") OLE study or enter a parent study OLE period. If entering the parent study OLE period, they will be required to complete the uptitration period (a minimum 36 weeks) following which they will then be able to roll over to the

POSTGRADUATE OLE study. This second option is for participants at sites where POSTGRADUATE is not yet approved when they have reached the end of the double-blind treatment period.

China Enrollment Plan

Based on historical data, participant recruitment is expected to take longer in China and therefore, a specific China enrollment plan has been established. Thus, if at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the National Medical Products Administration (NMPA) during the global enrollment phase, additional participants may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. Only participants enrolled at NMPA-recognized sites, during the global enrollment phase, will be included in the primary analysis. All participants enrolled at NMPA-recognized sites, either during the global enrollment phase or the China extension phases, will be included in a China-specific analysis.

The China-specific analysis will be described in a separate SAP and therefore is not covered in this document.

1.2.1 Treatment Assignment and Blinding

Randomization will be performed centrally using an interactive voice or Web-based response system (IxRS). After screening, participants who meet all eligibility criteria will be randomly assigned to one of two treatment groups (active drug or placebo). The ratio will be 1:1; one active to one placebo. The randomization method will be stratified block-randomization. Randomization to treatment allocation will be stratified by geographic region (Western Europe and Australia vs. Rest of the World vs. North America), participant APOE ε4 status (carrier vs. non-carrier), participant stage of disease (prodromal vs. mild AD), use of AD medication (presence vs. absence), and participation in the longitudinal amyloid and tau PET substudies. Except in circumstances in which a Health Authority, Ethics Committee, or Institutional Review Board requires it, a participant will not be told of his or her APOE ε4 status. Individual participant APOE ε4 genotype results will be blinded to participants, Investigators, and the Sponsor. APOE ε4 status information will be supplied directly to the IxRS vendor by the central testing laboratory so that the information can be incorporated at the time of randomization. For participants for whom APOE ε4 status is already known, the results will be blinded to the Sponsor and, as much as possible, to the site and central MRI reader.

The study is to be conducted in a double-blind manner to minimize potential bias from Investigators and participants. The Sponsor will be blinded to study treatment. In the OLE phase, the Sponsor, participants, and site staff will remain blinded to previous treatment allocation.

The randomization method implemented in the China extension cohort will be the same as that implemented in the global population.

1.2.2 Independent Review Facility

MRI scans will be reviewed by a central MRI core laboratory, which will perform the diagnostic reads and assessment of MRI outcome measures.

Central facilities will be used for PET assessments (see Independent Review Charter [IRC]).

1.2.3 Data Monitoring Committee

The iDMC will evaluate participant safety and efficacy on a regular basis. In addition to the data defined in the iDMC Charter (e.g., the incidence and nature of adverse events [AE], serious adverse events [SAE], adverse events of special interest [AESI], amyloid-related imaging abnormalities-edema/effusion [ARIA-E], amyloid-related imaging abnormalities-hemosiderin deposition [ARIA-H], and injection-site reactions [ISR]), the iDMC will review all necessary cumulative data at regular intervals during the study, including efficacy when needed. It is anticipated that these assessments will occur approximately every 3 months. At the time of each review, the iDMC will make appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, the treatment regimen should be modified, the protocol should be amended, enrollment should be held pending further safety evaluations). The iDMC will also evaluate planned or unplanned interim analyses for efficacy or futility.

2. STATISTICAL HYPOTHESES

The primary efficacy analysis will compare the active drug arm to the placebo arm at Week 116 with a two-sided test corresponding to the following null hypothesis, H_0, and alternative hypothesis, H_1:

$$H_0: \mu_{active} = \mu_{placebo}$$

$$H_1: \mu_{active} \neq \mu_{placebo}$$

Where μ_{active} and $\mu_{placebo}$ are the mean change from baseline to Week 116 in the CDR-SB score for each arm.

3. SAMPLE SIZE DETERMINATION

Determination of sample size is based on participants enrolled in the global enrollment phase. In each study, approximately 1016 participants will be enrolled and randomized in 1:1 ratio to each treatment arm (active drug or placebo) during the global enrollment phase. The original planned sample size was of 760 participants, but it was increased to 1016 participants based on considerations from external studies (in protocol version 3).

Additional participants may be randomized during the China extension if at least 1 participant is enrolled at sites in mainland China, Hong Kong, or Taiwan that are recognized by the NMPA during the global enrollment phase.

The estimated sample size required to demonstrate efficacy with regard to Clinical Dementia Rating-Sum of Boxes (CDR-SB) is based on the following assumptions:

- the mean change in the CDR-SB from baseline to Week 104 is 2.5 points in the placebo arm
- a common standard deviation across treatment arms for change of approximately 2.97 from baseline to Week 104 in the CDR-SB
- active drug has a true effect of a 30% relative reduction in deterioration of CDR-SB

Based on these assumptions, and using a student's T-test with equal variance, a sample size was calculated for 90% power to detect a true treatment effect of 30% relative reduction in deterioration of CDR-SB at a two-sided α of 0.05.

Uncertainties on parameters affecting the power (e.g., dropout rate, study drug discontinuation rate, standard deviation, and placebo decline) were assumed to be equivalent to a drop in sample size of up to around 35% and were corrected for accordingly. This calculation leads to a total of 1016 participants in the study.

At the date of writing Protocol Version 4, it was expected that participants would miss an average of 8 weeks of study drug administration over the course of the original two-year study due to the COVID-19 pandemic. This had the potential to decrease the power of the study from ~90% to ~80%. To mitigate the impact of missed administrations, the double-blind treatment period has been extended by 12 weeks. Under current assumptions, this brings the study power back to the originally planned ~90%.

4. ANALYSIS SETS

The following analysis sets are defined:

Table 2 Analysis Sets

Analysis set	Definition	Scope
All enrolled participants	All participants randomized during the global enrollment phase whether or not the participant received the assigned treatment. Analysis using this analysis set will be performed by randomized treatment.	Participant disposition report will be based on this analysis set
Intent-to-treat (ITT)	All participants randomized during the global enrollment phase, who received at least one dose of study drug. Analysis using this analysis set will be performed by randomized treatment.	All efficacy analyses, including the primary estimand, will be based on this analysis set.
CSF modified intent-to-treat (CSF-mITT)	All participants in the ITT analysis set who had at least one valid quantitative cerebrospinal fluid (CSF) measurement Analysis using this analysis set will be performed by randomized treatment.	All analyses of CSF biomarkers will be based on this analysis set
CSF-longitudinal	All participants in the CSF-mITT who had at least one valid quantitative Week 116 CSF measurement of phosphorylated tau (pTau-181), tTau or NFL.	Summary of treatment group comparability will also be repeated on this analysis set.
Plasma-longitudinal	All participants in the ITT analysis set who had at least one valid quantitative post-baseline plasma measurement of Amyloid beta (1-42) (Abeta-42) or phosphorylated tau (pTau-181)	Summary of treatment group comparability will also be repeated on this analysis set.
MRI modified intent-to-treat (MRI-mITT)	All participants in the ITT analysis set who had at least one valid volumetric MRI quantitative measurement. Analysis using this analysis set will be performed by randomized treatment.	All analyses of volumetric MRI parameters will be based on this analysis set.
MRI-longitudinal	All participants in the MRI-mITT with at least one valid post-baseline volumetric MRI quantitative measurement.	Summary of treatment group comparability will also be repeated on this analysis set.
Tau PET modified intent-to-treat (Tau-PET-mITT)	All participants in the ITT analysis set who participated in the Tau PET sub-study and who had at least one Tau PET scan with a valid quantitative measurement and who did not withdraw from the Tau PET substudy before randomization Analysis using this analysis set will be performed by randomized treatment.	All analyses of Tau PET parameters will be based on this analysis set.
Tau-PET-longitudinal	All participants in the Tau-PET-mITT with a valid post-baseline quantitative Tau PET measurement.	Summary of treatment group comparability will also be repeated on this analysis set.

Table 2 Analysis Sets (cont.)

Analysis set	Definition	Scope
Amyloid PET modified intent-to-treat (Amyloid-PET-mITT)	All participants in the ITT analysis set who participated in the Amyloid PET sub-study and who had at least one Amyloid PET scan with a valid quantitative measurement performed with either florbetaben or flutemetamol and who did not withdraw from the Amyloid PET substudy before randomization. Analysis using this analysis set will be performed by randomized treatment.	All analyses of Amyloid PET parameters will be based on this analysis set
Amyloid-PET-longitudinal	All participants in the Amyloid-PET-mITT with a valid post-baseline quantitative amyloid PET measurement performed with either florbetaben or flutemetamol.	Summary of treatment group comparability will also be repeated on this analysis set.
Safety-evaluable	All participants randomized during the global enrollment phase who received at least one dose of study drug. Any participant randomized to placebo who received at least one dose (any dose) of active drug will be summarized as having received the active drug. Analysis using this analysis set will be performed by treatment actually received.	All safety analyses (with the exception of Safety MRI) will be based on this analysis set.
MRI Safety-evaluable	All participants in the Safety-evaluable analysis set who had at least one post-baseline safety MRI scan. Analysis using this analysis set will be performed by treatment actually received	All analyses of safety MRI will be based on this analysis set.
Amyloid-PET Safety Evaluable	All participants in the Safety-evaluable analysis set who received at least one dose of radioligand Analysis using this analysis set will be performed by treatment actually received	All safety analysis for the amyloid-PET sub-study will be based on this analysis set.
Tau-PET Safety Evaluable	All participants in the Safety-evaluable analysis set who received at least one dose of radioligand. Analysis using this analysis set will be performed by treatment actually received	All safety analysis for the tau-PET sub-study will be based on this analysis set.

5. STATISTICAL ANALYSES

5.1 GENERAL CONSIDERATIONS

The clinical cutoff date for the primary analysis is defined by the date of the last randomized participant plus 116 weeks.

In the following sections, for all continuous variables for which descriptive statistics are indicated, the following statistics will be reported: the number of observations, the mean, median, standard deviation, and minimum and maximum. The 25th and 75th percentiles

(Q1 and Q3) will also be reported for selected tables. Descriptive summaries of discrete data will include frequencies expressed in terms of number and percentage of participants.

For clinical endpoints and biomarkers assessments, the baseline is defined as the assessment taken at the baseline visit (Day 1) up to and including the day of first study drug intake. If no assessment is reported at the baseline visit up to the day of first study drug intake, the earliest assessment reported after Day 1 and up to the day of second dose or Day 35, whichever is earlier, will be used as baseline. If no assessment is reported either at baseline visit or up to Day 35, an assessment reported at screening will be used as baseline. Day 35 is the latest timepoint allowed for Week 4 visit as per protocol.

For all other assessments, the baseline is defined as the last available assessment prior to first study drug intake, unless specified otherwise.

For biomarkers (CFS and plasma), values below the lower limit of quantification (LLOQ) will be set to 0.5*LLOQ, while values above the upper limit of quantification (ULOQ) will be set to ULOQ. A summary table will be provided to summarize the values below LLOQ and above ULOQ for each treatment arm.

The efficacy analyses will be based on the ITT analysis set (see Table 2) and will compare the active drug arm against the placebo arm with regards to mean change from baseline to Week 116. Two-sided test hypotheses will be defined in the following sections and the type I error level will be 5%. There are two identical Phase III studies, for each respective study the type I error level will be 5%. In order to protect the overall type I error rate (i.e., at each study level) when incorporating the hypothesis testing of multiple endpoints into the analysis, a fixed sequence testing procedure (Westfall and Krishen 2001) will be used to adjust for multiple comparisons. Testing of each hypothesis will follow a pre-specified order such that an endpoint would only be tested if the preceding one in the hierarchy was significant at 5% alpha level. The endpoint hierarchy, starting with the primary endpoint and including only confirmatory secondary endpoints, is the following:

1. CDR-SB (Clinical Dementia Rating, Sum of Boxes)
2. ADAS-Cog 13 (Alzheimer's Disease Assessment Scale, Cognitive subscale, 13-item)
3. ADCS-ADL (Alzheimer's Disease Cooperative Study, Activities of Daily Living scale) total score
4. FAQ (Functional Activities Questionnaire)

Missing outcome data will be handled using data imputation aligned with the estimand, see Section 5.3.3 for a detailed description of the analysis strategy.

When using a statistical model with baseline covariate adjustment, missing baseline covariate data other than the baseline outcome measure will be imputed to the overall median value for continuous covariates, or will be imputed to the most frequent category for categorical variables. In addition, baseline covariates will be derived from information collected into the eCRF, unless otherwise specified.

In statistical models using change from baseline of a given outcome measure as the dependent variable, there will be no imputation of the baseline outcome value, with the consequence that participants missing the baseline outcome measure will not contribute to the analysis.

The impact of the COVID-19 pandemic on the study and its conduct will be monitored and the overall impact will be assessed and described in the Clinical Study Reports.

5.2 PARTICIPANT DISPOSITION

The analysis of participant disposition will be based on all enrolled participants (see Analysis sets in Table 2). The number of participants enrolled will be tabulated by country, site, and treatment arm. Participant disposition (the number of participants randomized and completing the different study periods) will be tabulated by treatment arm. Premature study drug discontinuation and study discontinuation, as well as reasons for discontinuations, will be summarized.

Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm. Separate tables will be provided for COVID-19-related major protocol deviations and reasons for COVID-19-related major protocol deviations.

5.3 ENDPOINT ANALYSIS

5.3.1 Definition of Primary Endpoint

As detailed in the study protocols, the primary endpoint is the change from baseline to Week 116 in the CDR-SB which is a global scale covering both functional and cognitive domains.

The CDR-SB is a detailed quantitative general index that is scored from 0 to 18 with higher scores indicating greater impairment. The CDR characterizes six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The necessary information to make each rating is obtained through a semi-structured interview with the patient and a reliable informant or collateral source (e.g., a study partner).

5.3.2 Definition of Primary Estimand

The clinical question of interest is to assess the effect of the active drug on disease progression at Week 116, irrespective of use or initiation of symptomatic treatments for AD, in the absence of a substantial impact of the COVID-19 pandemic.

In alignment with the Addendum to ICH E9, the primary efficacy estimand is described by the following attributes:

- **Target Population**:
  Early (prodromal to mild) AD population as identified by the inclusion and exclusion criteria, see Sections 4.1.1 and 4.1.2 of the study protocols
- **Variable**:
  Change from baseline to Week 116 in Clinical Dementia Rating – Sum of Boxes (CDR-SB)
- **Treatment**:
  Prescribed study drug including uptitration to the target dose and safety-related dose modifications, irrespective of use or initiation of symptomatic treatment for AD
- **Population-level summary**:
  Difference in variable means between treatment arms

Intercurrent events (ICE):

The ICEs are classified into two categories: those that are Study Drug or Condition Related (SDCR) and those that are not (NSDCR). The list of main anticipated ICEs, and their classification as SDCR or NSDCSR, is presented below (Table 3). The final list of ICEs may need to be adapted in case unanticipated ICEs emerge during the study conduct. The classification of each ICE into SDCR or NSDCR will be completed and documented prior to the unblinding.

The ICE of substantial reduction in drug exposure due to the COVID-19 pandemic is defined as 4 or more dose-months (i.e., 16 weeks, not necessarily consecutive) of treatment missed due to COVID-19-related reasons. This definition will be equally applied to placebo and active arms. One dose-month is defined as 4 weeks of dosing, i.e., one dose with a Q4W dosing frequency (mostly during uptitration) or two doses with a Q2W dosing frequency (at target dose). The threshold of four missed dose-months was determined based on the following reasons:

– A 12-week extension to the study was implemented (in protocol amendment version 4) to mitigate the impact of the COVID-19 pandemic. Therefore, treatment interruptions up to 3 dose-months (i.e., 12 weeks) are already accounted for in the study design.

– Based on the half-life of approximately 24 days of gantenerumab, plasma concentration after a 4 months' interruption at the target dose is expected to be below the observed concentration with the dose of 225 mg Q4W which was

shown to be ineffective in Studies WN25203 (SCarlet RoAD) and WN28745 (Marguerite RoAD).

– A 20% difference is the usual acceptability threshold to establish PK bioequivalence. The protocol includes 20 dose-months (80 weeks) at target dose after the up-titration period. Missing less than 4 dose-months results in an overall reduction in drug exposure of less than 20% of the total planned dose.

As a conservative approach, all withdrawals from study treatment due to an AE will be classified as SDCR for the purpose of the primary analysis. This includes withdrawal from study treatment due to suspected or confirmed COVID-19 infection AE, because the relationship of these events to the participant condition may be ambiguous.

All SDCR ICEs will be handled with a treatment policy strategy, while NSDCR ICEs will be handled with a hypothetical strategy. The frequencies of ICE will be summarized by treatment arm.

In this study, given the disease stage at baseline of the target population, death is expected to be a rare event and mostly not considered related to treatment or disease progression, and as such the corresponding ICE of death will be handled with a hypothetical strategy for the primary estimand. Of note, a supplementary estimand which defines all ICEs, including death, as SDCR (and thus using the same imputation strategy as for the other SDCR ICEs; see Section 5.3.3), is described in Section 5.3.5.

Table 3 Intercurrent Events Impacting Primary Analysis

Intercurrent Event	SDCR/NSDCR	Estimand Approach
Withdrawal from study treatment due to lack of efficacy	SDCR	Treatment Policy
Withdrawal from study treatment due to safety or tolerability reason (NOTE: This will include discontinuation due to AE, incl. suspected or confirmed COVID-19 AEs)	SDCR	Treatment Policy
Withdrawal from study treatment with no informative reason given	SDCR	Treatment Policy
Withdrawal from study treatment due to the COVID-19 pandemic	NSDCR	Hypothetical Strategy
Substantial reduction in drug exposure due to the COVID-19 pandemic (defined as $\geq$ 4 missed dose-months)	NSDCR	Hypothetical Strategy
Withdrawal from study treatment due to purely administrative reason	NSDCR	Hypothetical Strategy
Death	NSDCR	Hypothetical Strategy
Withdrawal from study treatment due to use or initiation of protocol prohibited medication	SDCR	Treatment Policy
Withdrawal from study treatment due to other SDCR ICEs	SDCR	Treatment Policy

AE = adverse event; COVID-19 = coronavirus disease 2019; NSDCR = Non Study Drug or Condition Related; SDCR = Study Drug or Condition Related

ICE Derivation

Identification and categorization of the ICEs will be done based on fully blinded data only and will be finalized before database lock.

The number of missed dose-months due to the COVID-19 pandemic will be derived from the standardized eCRF data fields. More specifically, any Q4W missed dose due to COVID will count as 1 missed dose-months, while any Q2W missed dose due to COVID will count as 0.5 missed dose-months. The information whether a dose was missed due to COVID will be derived from the corresponding “reason for missed visit” and “reason for missed dose” fields in the eCRF.

All occurrences of “withdrawal from study treatment” ICE, as per Table 3, will be identified and categorized as SDCR/NSDCR based on the standardized reason reported in the eCRF “Study Drug Completion/Early Discontinuation” form. In case of ambiguity (i.e., if the reason for study drug discontinuation as reported in the eCRF is either “Protocol deviation”, “Withdrawal by subject”, “Physician decision” or “Other”), an adjudication committee will review the dedicated eCRF free text field and assign the withdrawal to a pre-specified ICE and a corresponding SDCR or NSDCR category. The

adjudication committee may also introduce additional ICEs to the list, in case where no appropriate fit is found in Table 3 or Appendix 2. The adjudication committee members must not have been involved in the conduct of Studies GRADUATE I and GRADUATE II and must not have been exposed to unblinding data from these studies. The members of the adjudication committee must have signed the charter of the adjudication committee, in Appendix 3.

5.3.3 Main Analytical Approach for Primary Estimand and Primary Endpoint

Primary study hypothesis

The primary efficacy analysis for this study will test the superiority of the active drug over the placebo at Week 116 with a two-sided test corresponding to the following null hypothesis, H_0, and alternative hypothesis, H_1:

$$H_0: \mu_{active} = \mu_{placebo}$$

$$H_1: \mu_{active} \neq \mu_{placebo}$$

Where μ_{active} and $\mu_{placebo}$ are the mean changes from baseline to Week 116 in the CDR-SB score for each arm.

Time Windowing

For the primary endpoint (and in general for clinical efficacy endpoints) the following time windows will be used for analyses (see Table 4), based on study days. Study days are defined based on days on study since the date of the first dose, with the day of the first dose being study day 1.

Table 4 Time windows for clinical endpoint assessments

Visit	Target day	Time window (in study days*)
Baseline	1	Up to Day 35
Week 24	169	72, 266
Week 52	365	267, 448
Week 76	533	449, 630
Week 104	729	631, 770
Week 116	813	771, earliest between 897 or first dose of OLE

In cases where more than one assessment falls within a time window, the assessment with the date closest to the target day is selected whether it's a scheduled, unscheduled or an early termination visit.

With regards to an ICE of withdrawal from study treatment, an assessment will be regarded as having happened after the ICE of withdrawal from study treatment if it is collected $>$28 days since the last dose.

General strategy to address the ICEs

For the primary estimand, a treatment policy approach will be used for all SDCR ICEs. In line with the clinical question of interest, the aim is to estimate a treatment effect irrespective of the occurrence of these ICEs. This approach is largely in line with the EMA guideline on the clinical investigation of medicines for the treatment of AD (EMA 2018).

All NSDCR ICEs will be handled using a hypothetical approach. The aim is to estimate a treatment effect "as if" the ICE had not happened. Post-ICE outcome values compatible with a hypothetical strategy are not directly observable. Consequently, any observed outcome values after NSDCR ICEs will be removed and treated as missing data for analysis purposes.

For participants with multiple ICEs, the type of the first ICE will determine the strategy to be considered.

Missing data assumptions for the primary estimator

For intermittent missing data (i.e., for participants with non-missing Week 116 data but missing data at other visits), missing data not associated with an ICE (e.g., for participants who had completed Week 104 visit before protocol v4 was implemented), and for missing data after NSDCR ICEs (handled with a hypothetical strategy), the missing data are assumed to be similar to those from the other participants in the same treatment group with no such missing data. This is compatible with a missing-at-random (MAR) assumption.

All observed data after SDCR ICEs will be included in the analysis. If data after SDCR ICEs are missing, they will be assumed to be similar to those in the placebo group for both study arms. Specifically, data will be imputed based on the placebo arm using reference based imputation with a Copy Increments from Reference (CIR) assumption (Carpenter et al, 2013 and Cro et al, 2020). This approach appears conservative yet plausible for the study drug. CIR assumes that changes in the primary endpoint after the ICE in a participant randomized to active drug can be represented by, i.e., imputed from, that of participants randomized to placebo. It therefore assumes no treatment effect after the ICE. In the placebo arm, this is compatible with a MAR assumption whereas in the active drug arm, the imputation is under a Missing Not At Random (MNAR) assumption.

Further details about the implementation of the missing data imputation are provided below. Sensitivity analyses for the missing data assumptions are discussed in Section 5.3.4.

Description of the primary estimator

The primary estimator will be applied to the ITT analysis set (see Table 2) and it will be implemented using four steps. First, an imputation model will be fitted to the data. Second, imputation of missing data will be performed based on the parameter estimates from the imputation model. Third, the completed data will be analyzed using an analysis of covariance (ANCOVA) model. Finally, inference will be performed based on resampling techniques. All four steps are described and justified in a published manuscript (Wolbers et al. 2022) which provides a more detailed justification of the statistical methodology and supportive simulations. Considerations about the control of type-I error for the primary estimator and supportive simulations, mimicking the setting of the GRADUATE I and GRADUATE II studies and exploring an extended range of plausible scenarios for missing data, are provided in the Appendix 1.

1. Imputation model

The imputation model is a mixed effects model for repeated measures (MMRM) with the longitudinally assessed change from baseline in CDR-SB as the dependent variable. Its purpose is to estimate mean trajectories and covariance matrices of longitudinal outcomes in the placebo and active drug arms, respectively, while subjects remain on their randomized treatment. Therefore, all data after withdrawal from study treatment will be removed and considered as missing for the purpose of estimating the imputation model, and for this purpose only. If these data were not excluded, then the imputation model would estimate mean trajectories based on a mixture of observed pre- and post-discontinuation data. These would not be compatible with the CIR assumption employed in the subsequent imputation step, which requires combining mean trajectories while on active drug up to the ICE with increments while on placebo thereafter, respectively.

The imputation model includes the following covariates: treatment group, visit, and treatment-by-visit interaction, baseline CDR-SB score and baseline CDR-SB score-by-visit interaction, baseline ADAS-Cog 13 total score, baseline ADCS-ADL total score and the randomization stratification factors, namely: disease stage (from the eCRF), geographic region (from the IxRS), the use of AD medication at baseline (derived from the eCRF based on a search of medications; see below for more details) and the APOE ε4 status (from the Vendor). For geographic region, IxRS is preferred over the eCRF source, to keep the “starting” region for analysis, in case a participant moved to a different region during the study (the eCRF would otherwise reflect the “final” region). AD medication at baseline will be defined as any use of donepezil, galantamine, memantine or rivastigmine prior to randomization and with an

end date not before the randomization date. An unstructured variance-covariance structure will be applied to model the within-subject errors across visits. If the model fails to converge, then a heterogeneous Toeplitz covariance structure will be used instead and if this still fails, then a compound symmetry covariance structure will be used.

Imputations will be based on restricted maximum likelihood (REML) estimation of the regression and covariance parameters from the imputation model (von Hippel and Bartlett 2021; Wang and Robins 1998).

2. Imputation step

The imputation model implies a marginal multivariate normal distribution of the longitudinal outcome values across all visits based on a participant's assigned treatment arm and covariate values. This marginal imputation distribution will be used for all participants in the placebo arm and all participants in the active drug arm without an SDCR ICE. For participants in the active drug arm with an SDCR ICE, the mean of the marginal imputation distribution for outcomes after the SDCR ICE will be modified as per the CIR assumption (Carpenter et al. 2013).

For each participant, the conditional imputation distribution of their missing outcome values is defined as the marginal imputation distribution conditional on the participant's observed outcomes (including observed post-SDCR ICE outcome assessments). A single deterministic imputation using the conditional mean from the conditional imputation distribution for each participant with missing outcomes will be used.

3. Analysis step

The completed data (using conditional mean imputation as described above) will be analyzed using an ANCOVA model with the change from baseline in CDR-SB at the Week 116 visit as the dependent variable. This analysis model includes treatment group as the primary covariate with adjustment for the same set of covariates as for the imputation model described above, namely baseline CDR-SB score, baseline ADAS-Cog 13 total score, baseline ADCS-ADL total score and the randomization stratification factors namely: disease stage (from eCRF), geographic region (from the IxRS), the use of AD medication at baseline (derived from eCRF based on a search of medications; see below for more details) and the APOE ε4 status (from the Vendor). For geographic region, IxRS is preferred over the eCRF source, to keep the "starting" region for analysis, in case a participant moved to a different region during the study (the eCRF would otherwise reflect the "final" region). AD medication at baseline will be defined as any use of donepezil, galantamine, memantine or rivastigmine prior to randomization and with an end date not before the randomization date. The primary treatment effect estimator is defined as the regression coefficient associated with the treatment group. The treatment effect will be reported as a difference in adjusted means. The treatment

effect at the other visits will be estimated in the same way and will be reported as supplementary analyses of the primary endpoint (see Section 5.3.5).

Percent relative difference, defined as 100 times the estimated treatment effect divided by placebo arm estimate, will also be reported, for all visits, as a point estimate for descriptive purposes. Importantly, ANCOVA is applied to a complete dataset after appropriate missing data imputation. For complete data, ANCOVA applied to outcomes from a single visit is equivalent to a more complex MMRM model. It can be demonstrated that it leads to identical parameter estimates as a corresponding MMRM model with an arbitrary covariance structure if separate regression coefficients are estimated at different visits for all covariates (Amemiya 1985, p. 197).

4. Inference step

Inference will be based on resampling techniques as recommended by von Hippel and Bartlett 2021. Specifically, the jackknife (Efron and Tibshirani, 1994) will be used to estimate the standard error of the primary treatment effect estimator and the test of the primary statistical hypothesis will be based on the corresponding *Z*-score. Compared to other resampling techniques, the jackknife has the advantage of providing a deterministic standard error estimate and, hence, removing any simulation randomness from the procedure.

5.3.3.1 Software Implementation and Validation

The reference based imputation methodology will be implemented by an internally developed R package "rbmi" ("reference-based multiple imputation"). The package will comply with the ICH guidance document "ICH E 9: Statistical principles for clinical trials" which states that: "The computer software used for data management and statistical analysis should be reliable, and documentation of appropriate software testing procedures should be available."

The testing strategy for the package consists of defining and documenting the expected input and output of each function and implementing unit tests to prove that the package performs as expected. All implemented methods will be recorded and referenced against the literature with unit tests and simulations put in place to show that known values can be recovered as well as showing consistency with similar software from other languages (most notably the "5-Macros" implemented by the Drug Information Association Scientific Working Group on Estimands and Missing Data in SAS).

The package, including all documentation and testing materials, is available on GitHub.com (https://github.com/insightsengineering/rbmi) and on CRAN repository (https://cran.r-project.org/package=rbmi) to allow for unrestricted access and enable public scrutiny of the code and methods. Description of the rbmi package is also available on a published manuscript (Gower-Page et al. 2022).

The rbmi R package was validated by the in-house tool, Autovalidate R, which performs general R package quality checks and performs testing for expected behaviors.

5.3.4 Sensitivity Analyses for Primary Endpoint

Impact of COVID-19 pandemic

The following sensitivity analyses will be performed to evaluate the impact of the COVID-19 pandemic:

- Vary threshold on number of missed dose-months due to the pandemic in the definition of "substantial reduction in drug exposure" ICE. The "substantial reduction in drug exposure" ICE is defined with a threshold $\geq$ 4 dose-months (not necessarily consecutive). A sensitivity analysis will be performed using different thresholds: 1, 2, 3, 5 and 6 dose-months. All other aspects of the primary estimator will remain the same.
- Exclude participants based on site closure information and apply a treatment policy strategy to all other COVID-19 related ICEs. In this analysis, all participants enrolled before a site closure due to the pandemic will be removed from the analysis set. In alignment with the primary estimand, only a site closure of 16 weeks or more during the double-blind treatment period and without any access to study drug (no home nursing) will be considered. In accordance with the FDA's guidance for Industry "Statistical Consideration for Clinical Trial During the COVID-19 Public Health Emergency (June 2020)", participants excluded from this analysis can be identified using baseline data only: randomization date and site number. The site closure information is an administrative site level information, independent of the conduct of the trial, collected using the eCRF for the purpose of this study and analysis. The substantial reduction in drug exposure due to the COVID-19 pandemic (defined as $\geq$ 4 missed dose-months) will not be considered as an ICE. All other aspects of the primary estimator will remain the same.
- Remote scale administration. Remote scale administration was authorized in exceptional cases at Weeks 104 and 116 visits due to COVID-19 related restrictions. In this analysis, all CDR-SB assessments performed remotely will be excluded from the analysis and treated as missing data. All other aspects of the primary estimator will remain the same.
- A subgroup analysis based on the date of randomization. This will allow estimating the treatment effect for subgroups of participants randomized at least 12 months before the onset of the global COVID pandemic (11 March 2020 according to the World Health Organization (WHO) opening remarks), in $\geq$5 to 12 months prior to the onset of the global COVID pandemic and within less than 5 months from the onset of the global COVID pandemic (see Section 5.3.5.1 for an exact definition of each subgroup).

Impact of missing data handling methods

The following sensitivity analyses will be performed to evaluate the impact of missing data handling method:

– Tipping point analysis

This analysis stress tests the CIR assumption by imputing worse outcomes after SDRC ICEs in the active drug arm than predicted by the CIR assumption. This will be implemented via a marginal δ-approach as described in the 'rbmi: advanced functionality' vignette of the rbmi's package and in Cro et al, 2020. Specifically, the imputation step will be performed as for the primary estimator and, after imputation is completed, a constant δ will be added to the imputed week 116 outcomes occurring after SDCR ICEs in the active drug arm. The subsequent analysis step of these δ-adjusted imputed datasets is as for the primary estimator.

To determine the tipping point, the constant δ will be increased in small steps starting from a value of 0 (corresponding to the primary estimator). The tipping point will then be defined as the value of δ at which the p-value for the treatment effect estimator first becomes greater than 5%.

Impact of potential outliers or extreme observations

In order to assess the impact of a potentially small number of "extreme observations" or "outlier points" (e.g., rapid progressors) on the treatment effect, the ANCOVA analysis model will be replaced by a robust linear regression. Robust regression will produce treatment effect estimates less contaminated by highly influential observations. Specifically, robust regression using M estimation will be used. Standard errors and confidence intervals will be based on jackknife as described previously.

5.3.5 Supplementary Analyses for Primary Endpoint

5.3.5.1 Subgroup Analyses for Primary Endpoint

The generalizability of the CDR-SB results when comparing the active drug arm to the placebo arm will be investigated by estimating the treatment effect in the following subgroups:

- Demographics:
  - Age, two age categories cut by the median
  - Sex
  - Geographic Region, as per IxRS
- Baseline disease severity:

  CDR-GS = 0.5 vs CDR-GS > 0.5
  - Prodromal vs Mild (as per eCRF)
- APOE ε4 genotype

    - Carrier/Non Carrier
- Use of symptomatic AD medication at baseline Yes/No (derived from eCRF based on the search below)
    - Symptomatic AD medication is defined as any one of: donepezil, galantamine, memantine or rivastigmine
- Randomization date, three subgroups defined by the following dates:
    - *before* 11 March 2019
    - *in between* (and including) 11 March 2019 and 1 October 2019
    - *after* 1 October 2019

Summaries of the treatment effect for the change in CDR-SB from baseline to Week 116 by these subgroups will be provided in forest plots.

5.3.5.2 Other Supplementary Analyses for Primary Endpoint(s)

Treatment effect estimates before Week 116

In this supplementary analysis, the same analysis strategy as described for the primary estimator will be used to estimate the effect of the active drug on disease progression defined as a change in CDR-SB at other time points, other than Week 116.

The treatment effect on the adjusted mean change in CDR-SB from baseline to Week 24, 52, 76 and 104 will be provided.

Treatment policy estimand

All ICEs will be handled with a treatment policy strategy regardless of whether being SDCR or NSDCR. All observed data will be included regardless of occurrence of any ICE. Missing values following all ICEs will be imputed with the method used in the primary estimator for missing data following an SDCR ICE, see Section 5.3.3. Missing values, not following an ICE, will be imputed under MAR (similarly to the primary estimands analysis, see "Missing data assumptions for the primary estimator" in Section 5.3.3). Note that the attributes of population, variables, treatment, and population level summary will remain the same as for the primary estimand.

Concomitant AD treatment estimand

In this supplementary analysis, the treatment effect will be evaluated in the hypothetical scenario that no post-baseline initiation or modification of the use of other approved AD medication has happened.

All attributes of this estimand except Treatment will be identical as for the primary estimator. The treatment attribute will be: "Prescribed study drug including uptitration to the target dose, irrespective of concomitant use of symptomatic treatment for AD at

baseline, but assuming no initiation or change in symptomatic treatment after baseline". In this supplementary analysis, all data following ICEs "Starting another treatment for AD" and "Changing the dose of a symptomatic treatment for AD" will be set to missing and imputed under a MAR assumption, in line with a hypothetical strategy. The analysis methods will be the same as described for the primary estimand.

MMRM

This analysis aims to provide a reference point analysis method described in early versions of the protocol (up to version 4) and to other external analyses where MMRM was considered the default and primary analysis. All available data will be used in the analysis. There will be no missing data imputation or consideration for any intercurrent events. The model will include the following covariates: treatment group, visit, and treatment-by-visit interaction, baseline CDR-SB score and baseline CDR-SB score-by-visit interaction, baseline ADAS-Cog 13 total score, baseline ADCS-ADL total score and the randomization stratification factors, namely: disease stage (from eCRF), geographic region (from the IxRS), the use of AD medication at baseline (from eCRF) and the APOE ε4 status (from the Vendor). An unstructured variance-covariance structure will be applied to model the within-subject errors across visits. In the case of non-convergence, compound symmetry will be used, together with a robust estimator of standard error ("sandwich" estimator).

Clinically evident decline: a progressor analysis

In this supplementary analysis, CDR-SB progression will be defined as a change from baseline in CDR-SB greater than or equal to a threshold x. The primary threshold of interest is $x = 2.5$. The work justifying the threshold will be presented, as an oral presentation, at the Alzheimer's Association International Conference (AAIC), 31 July–4 Aug 2022; San Diego, CA and online (title of the oral presentation: *Selecting appropriate meaningful change thresholds for trials of early (prodromal-to-mild) AD: A caregiver-rated, anchor-based analysis based on the Tauriel Study*).

The CDR-SB progression endpoint will be analyzed using the same conditional mean imputed dataset as for the primary estimator of the primary estimand (Section 5.3.3).

The probability of CDR-SB progression by Week 116, in each treatment arm, will be estimated by the proportion of participants with a progression at any time during the double blinded period. The probability of progression by Week 116 will be obtained for different values of the progression threshold x. A plot of the probability of CDR-SB progression by Week 116 versus threshold values x will be generated.

In addition, a Cox proportional hazard model to estimate the treatment effect on time to first CDR-SB progression (based on the primary threshold of interest), may also be considered. In this case, the same baseline covariates as for the primary estimator of the primary estimand will be used (Section 5.3.3). An unadjusted model or a stratified

analysis may be considered as well. Corresponding standard errors and confidence intervals will be calculated using the jackknife as previously described.

Impact of ARIA-E MRI finding on the primary outcome

In this supplementary analysis, the objective is to estimate the treatment effect, in the hypothetical scenario where ARIA-E would not have occurred. This analysis aims at removing the potential impact of ARIA-E on the primary endpoint.

All the attributes from the primary estimand will remain the same, but an ICE of 'ARIA-E occurrence' will be added. The 'ARIA-E occurrence' will be handled with hypothetical strategy. All data collected after the occurrence of an ARIA-E will be removed and treated as missing for this data analysis purpose. Post- ARIA-E data will then be imputed under the Missing at Random assumption unless ARIA-E is not the first ICE. In this case, the imputation will be determined by the strategy for the first ICE as described for the main estimator.

5.4 SECONDARY ENDPOINTS ANALYSES

The same primary estimand's analysis strategy will be applied to secondary endpoints listed in Table 4. For all continuous secondary endpoints, the ANCOVA analysis model will include the baseline score of the secondary endpoint, the disease stage, geographic region, the use of AD medication at baseline and the APOE ε4 status as covariates.

In the following, confirmatory secondary endpoints refer to endpoints included in the type I error control procedure. Other important secondary endpoints not subject to the type I error control procedure are considered as supportive secondary endpoints. For all secondary endpoints, the treatment effect over time will also be considered and the change from baseline to Weeks 24, 52, 76, and 104 will be provided as supplementary analyses.

Table 5 Secondary Endpoints

Secondary Efficacy Endpoint	Confirmatory	Type
Alzheimer's Disease Assessment Scale, Cognitive subscale, 13-item (ADAS-Cog 13)	yes	Continuous
Alzheimer's Disease Cooperative Study, Activities of Daily Living scale (ADCS-ADL) total score	yes	Continuous
Functional Activities Questionnaire (FAQ)	yes	Continuous
Mini Mental State Examination (MMSE)	no	Continuous
Alzheimer's Disease Assessment Scale, Cognitive subscale, 11-item (ADAS-Cog 11)	no	Continuous
Coding (Digit Symbol Substitution Test [DSST])	no	Continuous
Verbal Fluency Task	no	Continuous
Alzheimer's Disease Cooperative Study, Activities of Daily Living scale (ADCS-ADL) instrumental score	no	Continuous

ADAS-Cog 13= Alzheimer's Disease Assessment Scale, Cognitive subscale, 13-item; ADCS-ADL= Alzheimer's Disease Cooperative Study, Activities of Daily Living scale; ADAS-Cog 11 = Alzheimer's Disease Assessment Scale, Cognitive subscale; DSST= Digit Symbol Substitution Test; FAQ= Functional Activities Questionnaire; MMSE= Mini Mental State Examination.

5.4.1 Confirmatory Secondary Endpoints

The confirmatory secondary endpoints are provided to increase the confidence in the treatment effect observed on the primary endpoint. For these confirmatory secondary endpoints, the analysis method will be the same as for the primary endpoint. All estimand attributes except Variable (i.e., Target population, Treatment, Population-level summary) will be identical as for the primary estimator (see Section 5.3.1). The same ICEs and analysis methods will be used, see Section 5.3.3. For these confirmatory secondary endpoints, MMRM analyses will also be considered as supplementary analyses. In this case, the change from baseline in the confirmatory secondary endpoints will be adjusted on the following covariates: treatment group, visit, treatment-by-visit interaction, the respective baseline score for each secondary endpoint, the baseline score-by-visit interaction and the randomization stratification factors as specified for the primary endpoint, see Section 5.3.4, paragraph on MMRM.

The method for controlling the overall Type I error is described in section 5.1.

5.4.1.1 Alzheimer's Disease Assessment Scale, Cognitive Subscale, 11- item and 13-Item (ADAS-Cog 11/ ADAS-Cog 13)

The ADAS-Cog is the most frequently used scale to assess cognition in clinical trials for mild to moderate AD dementia (Rozzini et al. 2007; Connor and Sabbagh 2008; Ihl et al. 2012). More specifically, the ADAS-Cog is a participant-based assessment that measures learning and memory, language production, language comprehension, constructional praxis, ideational praxis, and orientation. The modified version will be used; it has 13 items and includes the addition of delayed word recall and a number of cancellation subtests, as well as use of only one trial for word recognition (Mohs et al. 1997). Equivalent alternate forms of the word recall, word recognition, and number cancellation subtests will be used in successive test administrations. The ADAS-Cog 11 and 13 will be used in this study, with ADAS-Cog 13 considered as a confirmatory secondary endpoint. Individual item scores are based on errors and generally range from 1 to 5, although some items have smaller or larger score ranges. The ADAS-Cog 13 total score ranges from 0-85, with higher scores reflecting greater impairment. It takes approximately 45 min to administer the ADAS-Cog 13.

5.4.1.2 Alzheimer's Disease Cooperative Study, Activities of Daily Living Scale (ADCS-ADL), Total Score

The ADCS-ADL (Galasko et al. 1997) is the scale most widely used to assess functional outcome in participants with AD (Vellas et al. 2008). The ADCS-ADL is a 23-item informant-based questionnaire that covers both basic activities of daily living (ADL) (e.g., eating and toileting) and more complex ADL or instrumental ADL (e.g., using the telephone, managing finances, preparing a meal). It has a 4-week recall period. Total scores range from 0-78, with higher scores indicating better functioning.

5.4.1.3 Functional Activities Questionnaire (FAQ)

The FAQ (Pfeffer et al. 1982) is an informant-based measure of functional abilities. Informants provide performance ratings of the target person on ten complex higher-order activities. The FAQ is a 30-point scale, the higher the score the worse the performance.

5.4.2 Supportive Secondary Endpoints

For context, additional clinical endpoints collected longitudinally in the studies will be provided (see Table 4). The Sponsor proposes not to rank these hierarchically as for confirmatory secondary endpoints.

5.4.2.1 Mini Mental State Examination (MMSE)

The MMSE is a set of standardized questions used to evaluate possible cognitive impairment and help stage the severity level of this impairment (Folstein et al. 1975). The questions target six areas: orientation, registration, attention, short-term recall, language, and constructional praxis/visuospatial abilities. The MMSE is a participant-based assessment. The score ranges from 0-30, with lower values indicating a greater impairment.

5.4.2.2 Digit Symbol Substitution Test (DSST)

Coding, also called Digit Symbol Substitution Test (or DSST), is a subtest from the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV; Wechsler 2008). Coding is a participant-based assessment that measures speed of processing and associative memory. The test is known to be sensitive to disease progression (Lezak et al. 2004). The 120-second version of the test will be used in this study.

5.4.2.3 Verbal Fluency Task

The category verbal fluency (e.g., animals) is a participant-based assessment that measures speed and flexibility of verbal thought. Verbal fluency tests are sensitive tools for detecting dementia (Pasquier et al. 1995; Lezak et al. 2004) and for monitoring decline over time (Clark et al. 2009).

5.4.2.4 Alzheimer's Disease Cooperative Study, Activities of Daily Living Scale (ADCS-ADL), Instrumental Score

The ADCS-ADL instrumental score is a sub score of the ADCS-ADL scale, see Section 5.4.1.2. The ADCS-ADL instrumental score used in this study is the sum of items 6a and 7 to 23.

5.4.3 COVID-19 Related Sensitivity Analyses for Secondary Endpoints

During the COVID-19 pandemic, many countries took movements' restriction policy. Among the clinical outcomes collected in the study, some questionnaires may be particularly impacted. These questionnaires include items describing actions that are strongly constrained or prohibited by restriction policies.

We define modified versions of the total score for these scales. These modified scales scores may be used to perform sensitivity analysis aiming at understanding and mitigating the impact of the COVID-19 pandemic on study results and interpretation, in line with the primary clinical question of interest.

5.4.3.1 ADCS-ADL COVID-19 Modified Total Score

The original ADCS-ADL is a 23 item scale with a total score range of 0-78. The following items were identified as being particularly impacted by the pandemic related restrictions:

- Item 2: Optimal walking performance, maximum 3 points
- Item 15: Optimal performance getting around/travelling outside the home, maximum 4 points
- Item 16a/b: Shopping trips - selecting items and paying without supervision, maximum 4 points
- Item 18: Left away from home, maximum 3 point

A sensitivity analysis may be conducted, using a modified version of the ADCS-ADL total score after removing of these four items, resulting in a 19-item scale with a score range of 0-64. This alternative version will be referred to as “ADCS-ADL COVID-19 modified total score”.

5.4.3.2 FAQ COVID-19 Modified Total Score

The original FAQ is a 10-item scale with a score range of 0-30. The following items were identified as being particularly impacted by the pandemic related restrictions:

- Item 3: Shopping alone, maximum 3 points
- Item 10: Travelling outside of the neighborhood, maximum 3 points

A sensitivity analysis may be conducted, using a modified version of the FAQ total score after removing of these 2 items, resulting in an 8-item scale with a score range of 0-24. This alternative version will be referred to as “FAQ COVID-19 modified total score”.

5.5 EXPLORATORY ENDPOINT(S) ANALYSIS

The same primary estimand’s analysis strategy will be applied to continuous exploratory endpoints listed in Table 6. For all continuous exploratory endpoints, the ANCOVA analysis model will include the baseline score of the exploratory endpoint, the disease stage, geographic region, the use of AD medication at baseline and the APOE ε4 status as covariates.

For ordinal endpoints, only descriptive analyses will be considered, summarizing the frequencies of the different categories, as well the proportion of participants with a certain shift in categories.

The Resource Utilization in Dementia Scale–Lite (RUD-Lite) and the EuroQoL–5 Dimensions (EQ-5D-5L) scales will be used in this study for informing pharmacoeconomic evaluations and will be reported separately.

Table 6 Exploratory Endpoints

Exploratory Efficacy Endpoint	Type
Clinical Dementia Rating-Global Score (CDR-GS)	Ordinal
CDR-Individual Components	Continuous
Dependency Level, as assessed by the Alzheimer disease cooperative study - activities of daily living (ADCS-ADL) score	Ordinal
Integrated AD Rating Scale (iADRS)	Continuous
Quality of Life–Alzheimer's Disease (QoL-AD)	Continuous
Neuropsychiatric Inventory Questionnaire (NPI-Q)	Continuous
Zarit Caregiver Interview–Alzheimer's Disease (ZCI-AD)	Continuous

ADCS-ADL = Alzheimer disease cooperative study-activities of daily living; ADCOMS = AD Composite Score; CDR-GS =Clinical Dementia Rating-Global Score; EQ-5D= EuroQoL–5 Dimensions; iADRS = Integrated AD Rating Scale; NPI-Q= Neuropsychiatric Inventory Questionnaire ; QoL-AD =Quality of Life–Alzheimer's Disease; ZCI-AD=Zarit Caregiver Interview–Alzheimer's Disease.

5.5.1.1 Clinical Dementia Rating–Global Score (CDR-GS) and Individual Components of the CDR scale

The Washington University CDR is a global assessment instrument that yields global scores (GS) and sum of boxes (SOB) scores. The CDR is derived from a semi-structured interview with the participant and an appropriate informant, and it rates impairment in six categories (Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care) on a 5-point scale for which 0 = no impairment, 0.5 = questionable impairment, and 1, 2, and 3 = mild, moderate, and severe impairment, respectively. From the six individual category ratings, or box scores, the CDR-GS is established by clinical scoring rules, for which CDR 0 = no dementia and CDR 0.5, 1, 2, or 3 = questionable, mild, moderate, or severe dementia, respectively (Morris 1993).

5.5.1.2 Dependence Level Assessed by the ADCS-ADL Score

To calculate dependence levels, scores on the ADCS-ADL can be transformed into discrete levels of disability via an algorithm developed initially by Kahle-Wrobleski (2015). Items from the ADSC-ADL were mapped to 6 levels of dependence derived from the Dependence Scale (Zhu et al., 2009), ranging from Level 0: no impairment in instrumental or basic ADLs to Level 5: complete incontinence or inability to transfer. Four subscales were used to aid the construction of dependence levels, including bADLs, domestic/household activities, communication/engagement and outside

activities. The mapping of items to dependence levels was validated using additional clinical and economic measures.

A revised algorithm, developed to a) remove ambiguity regarding the contribution of some items and b) add clarity on the handling of missing data, will be used to calculate the dependence levels. Progression to greater levels of dependence is indicative of disease progression and is informative for a variety of care providers and stakeholders. This algorithm is provided in appendix, see Appendix 2.

5.5.1.3 Integrated AD Rating Scale (iADRS)

The iADRS is a composite of cognition and function that combines scores from the ADAS-Cog-13 (cognition) and the instrumental component of the ADCS-ADL (function) (Wessels et al., 2018). A sum score of the total scores of both components is calculated (ADAS-Cog is reversed) using the following formula:

iADRS = [-(ADAS-Cog13) + 85] + ADCS-iADL.

Total score range from 0 to 141. The iADRS total score will be generated and results may be reported in the CSR.

5.5.1.4 AD Composite Score (ADCOMS)

The ADCOMS was developed to assess cognition and function in early stages of AD. It is a composite score that combines 12 items from existing AD measures, specifically the ADAS-Cog (Delayed word recall, Orientation, Word recognition, Word finding difficulty), MMSE (Orientation time and Constructional praxis) and all CDR-SB items (Wang et al., 2016). The ADCOMS score was built using a linear longitudinal model to characterize the relationship between disease progression and the individual items from existing AD clinical scales. A PLS regression procedure was used to identify individual clinical scale items that represent AD-related clinical decline over time to calculate their respective weighting factors. The resulting composite ADCOMS score is a weighted linear combination of the individual scale items selected in the fitted PLS model. Items with small contribution to the PLS model were removed according to Wold's criterion (a Variable Importance of Projection below 0.8). Total score range from 0 to 1.97, with lower scores indicating greater impairment. The ADCOMS total score will be generated and results may be reported in the CSR.

5.5.1.5 Quality of Life–Alzheimer's Disease (QoL-AD)

The Quality of Life-Alzheimer's Disease (QoL-AD) was developed to assess quality of life (QoL) in participants who have dementia (Logsdon et al. 1999, Logsdon et al 2002). The QoL-AD consists of 13 items covering aspects of participants' relationships with friends and family, physical condition, mood, concerns about finances, and overall assessment of QoL. The total score is the sum of the 13 items and ranges from 13 to 52, with higher scores indicating better health-related QoL. In this study, the QoL-AD will be administered in a standardized, structured interview format to participants by

investigative staff in order to gather participant responses about QoL. The study partner will also complete the study partner version of the questionnaire to enable proxy responses from the study partner.

5.5.1.6 Neuropsychiatric Inventory Questionnaire

The Neuropsychiatric Inventory-Questionnaire (NPI-Q) (Kaufer et al. 2000) was developed to assess a wide range of behaviors encountered in dementia participants, to provide a means of distinguishing severity of behavioral changes, and to facilitate rapid behavioral assessment through the use of screening questions. It is an informant-based instrument in which 12 behavioral domains are evaluated. The recall period is the past month, and severity scores range from 0 to 36, with higher scores indicating greater severity. The study partner's distress portion of the scale was not used in this study.

5.5.1.7 Zarit Caregiver Interview–Alzheimer's Disease (ZCI-AD)

The Zarit Caregiver Interview-Alzheimer's Disease (ZCI-AD) is a modified version of the Zarit Burden Interview 22-item version, which was originally designed to reflect the stresses experienced by caregivers for people with dementia (Zarit and Zarit 1990). The modified version includes modifications in item and title wording (e.g., removal of "your relative "to refer directly to the participant, removal of "burden" from title), inclusion of additional items, the use of 11-point numerical rating scales for each item and a 4 week recall period. The ZCI-AD measure consists of 27 items covering 13 domains (i.e., humanistic impact domain (14 items) including the domains physical (3 items), emotional (4 items), social (3 items), and daily life (4 items), and the additional domains exhaustion (2 items), dependence (2 items), worry (2 items), role perception (3 items), financial impact (1 items), difficulty with medication (1 item), overall difficulty of caregiving (1 item), and sadness (1 item)). The ZCI-AD is completed by the study partner without involvement from the site staff. The ZCI-AD is scored on a domain level with each domain score ranging from 0 to 100 with higher scores indicating higher level of impact. All item responses are re-coded on a 0 to 4 scale (response category 0=0; response category 1,2, and 3=1; response category 4,5,and 6=2; response category 7 and 8=3; response category 9 and 10=4) and items of a domain are summed up and transformed to 0 to 100 score range. Domain scores are only calculated if responses of at least 80% of items of the respective domain are available. The ZCI-AD has been validated in prodromal, mild and moderate stages of AD (Bernaards, C et al.)

5.6 SAFETY ANALYSES

Descriptive statistics will be used to analyze all safety data collected in the double-blind treatment period in the safety-evaluable analysis set, unless otherwise specified.

Safety data collected from the day of the first dose of blinded study drug up to 14 weeks after the last dose of blinded study drug (but no later than the day before the first OLE dose for the participants who entered the OLE period) will be included in the double-blind treatment period analyses. Non-treatment emergent safety data collected

beyond the 14-week post last dose period and until the end of the study will be included in the follow-up period analyses.

For participants who entered the OLE period, safety data collected from the day of the first OLE dose up to 14 weeks after the last OLE dose will be included in the OLE period analyses

Safety analyses will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results (including shift tables), MRI findings, changes in vital signs and ECGs, and changes in C-SSRS scores.

5.6.1 Extent of Exposure

Exposure to study drug information will be descriptively summarized by treatment as follows:

- Treatment duration (in weeks)
- Total number of administrations
- Total cumulative dose (mg)
- Number of dose-administrations at each dose level

5.6.2 Adverse Events

All verbatim AEs terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version that is current at the time of the analysis (Version 25.0 or higher), and AE severity will be graded according to the scale defined in Table 5 in Section 5.3.3 of the study protocol (mild/moderate/severe). For each treatment group, the frequency of each AE preferred term will be defined as the number of participants experiencing at least one occurrence of the event. Each table will present the overall number and percentage of participants experiencing at least one AE and the total number of AEs reported. Percentages will be based on the number of participants in the safety-evaluable analysis set. In summary tables, AEs will be sorted by body system (in decreasing order of overall incidence), then by preferred term (in decreasing order of overall incidence). The summary tables will be restricted to treatment-emergent AEs, i.e., AEs that occur on or after the day of first dose of study drug. Non-treatment-emergent AEs (with onset before the first dose) will be listed.

The following safety information will be summarized by treatment group for the double-blind treatment period:

- AEs, AEs by intensity, AEs related to study drug
- Deaths
- SAEs, SAEs related to study drug
- AEs leading to discontinuation of study treatment

- AEs leading to dose modifications (dose interruption, dose reduction or delayed up-titration). Delayed up-titration at any given visit is defined as the simultaneous occurrence of the following two tick-boxes in the eCRF Adverse Events form:
  - Action take with Gantenerumab due to AE/SAE: Dose Not Changed
  - Was dose regimen modified from protocol schedule? Yes"
- Injection site reaction (ISR) signs and symptoms
- Systemic injection reactions (AEs with eCRF tickbox “systemic injection reaction” selected)
- ‘Hypersensitivity reactions’

Protocol-specified adverse events of special interest (AESI) will be listed.

The impact of the COVID-19 pandemic on the safety data will be assessed by reviewing the following:

- Confirmed or suspected COVID-19 AEs
- AEs associated with COVID-19
- Potential long COVID-19 symptoms

The following data handling rules will be applied for all AE summary tables:

- Events that are missing both at onset and at end dates will be considered to have started after the first dose of study drug and the duration will be set to missing.
- If the onset date is missing, and the end date is on or after the first dosing date or unresolved or missing, then the event will be considered to have started after the first dose of study drug.

The following data handling rules will also be applied for specific tables:

- An AE will be included in the summary table of AEs leading to study drug discontinuation if the “action taken with blinded gantenerumab” drop-down menu on the AE eCRF is checked “drug withdrawn”.
- In the summary table of AEs by intensity, if a participant has more than one occurrence of an event, the event with the most severe intensity will be counted. If the intensity of an AE is missing, then the AE will be included only in the total number of events column, and not in the count of participants with the event by intensity.
- In the summary table of AEs related to study drug, if a participant has more than one occurrence of an event, the related event will be counted if applicable. If the relationship of an AE is missing, then the AE will not be included.

5.6.3 Magnetic Resonance Imaging Safety Findings

ARIA-E and ARIA-H are identified risks associated with gantenerumab. Sites were asked to capture all ARIAs as AEs in the eCRF that met any of the following criteria:

- Symptomatic ARIA-E (i.e., accompanied by CNS symptoms), and/or

- ARIA findings that result in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation), and/or
- Findings that are otherwise clinically significant in the investigator's judgment

Not all ARIA MRI findings qualify as AE. ARIA analyses will be mainly based on ARIA MRI findings. ARIA AEs will also be reported. Based on MRI data, the incidence, and severity (based on the Barkhof Grand Total Score [BGTS]) ARIA-E and the incidence of ARIA-H will be summarized by treatment group and within this also by APOE ε4 genotype (by number of alleles) and by dose level. Additionally, the timing of ARIA-E and the timing to meet the protocol-defined criteria for permanent discontinuation due to ARIA-H will be also summarized by descriptive statistics and eventually by Kaplan-Meier methods. Recurrence of ARIA-E will be summarized by treatment group and within this also by APOE ε4 genotype (by number of alleles). ARIA-E associated with CNS symptoms (see Section 5.6.3.1) and with serious CNS symptoms will be summarized by treatment group and within this also by APOE ε4 genotype. Temporal co-occurrence of ARIA-E and ARIA-H will be summarized by treatment group and within this also by APOE ε4 genotype (by number of alleles). Temporal co-occurrence is defined as an MRI scan showing new ARIA-H that occurs between ARIA-E onset and resolution (inclusive), irrespective of the brain region.

MRI findings other than ARIA will also be summarized.

5.6.3.1 CNS Symptoms Temporally Associated with ARIA-E MRI Findings

CNS symptoms temporally associated with ARIA-E are defined as onset or worsening of CNS symptom(s) that is/are temporally associated with ARIA-E MRI findings. CNS symptoms experienced by the participant that are new or worsened since the last MRI without ARIA-E are collected in a CNS Symptoms Request Form before the MRI takes place at a visit. To identify CNS symptoms temporally associated with ARIA-E MRI findings, the following definitions will be used:

NEW CNS symptoms: If there is any AE reported in the eCRF with "Reported on the MRI CNS symptoms request form" = Y that is [new since date of most recent MRI scan showing no ARIA-E findings] AND is [ongoing or ends between the date of most recent site visit prior to date of MRI scan showing new ARIA-E (MRI) and date of MRI scan showing ARIA-E resolution (MRI)] then ARIA-E should be classified as associated with CNS symptoms

OR

WORSENED CNS symptoms: If there is any AE reported in the eCRF with "Reported on the MRI CNS symptom request form" = Y that is [started before the date of most recent MRI scan showing no ARIA-E findings] AND is [ongoing or ends between the date of

most recent site visit prior to date of MRI scan showing new ARIA-E (MRI) and date of MRI scan showing ARIA-E resolution from MRI data] AND [there is an increase in severity grading] then ARIA-E should be classified as associated with CNS symptoms.

The CNS symptoms temporally associated with ARIA-E MRI findings will be listed and summarized by treatment group and within this also by APOE ε4 genotype (number of alleles).

5.6.4 Laboratory Data

Laboratory data will be summarized by treatment group for each assessment visit using descriptive statistics of absolute values and change from baseline values. In addition, the frequency of participants with abnormal laboratory values will be summarized by treatment group.

5.6.5 Vital Signs

Vital signs assessments include systolic blood pressure, diastolic blood pressure, and pulse rate measured throughout the study. Vital sign measurements will be summarized by treatment group for each assessment visit using descriptive statistics of absolute values and change from baseline values. In addition, the frequency of participants with abnormal results will be summarized by treatment group.

5.6.6 ECGs

ECG data will be summarized by treatment group for each assessment visit using descriptive statistics of absolute values and change from baseline values for the following parameters:

- Heart rate
- QRS duration
- RR interval
- PR interval
- QT intervals (including QTcF)

For QTcF, the summary will also include 2-sided 90% confidence interval at each time-point.

In addition, ECG overall interpretations will be summarized by treatment group and visit.

5.6.7 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is an assessment tool used to assess the lifetime suicidality of a participant (C-SSRS at baseline) as well as any new instances of suicidality (C-SSRS since last visit). The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual or potential lethality.

Suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent will be summarized by treatment group. In addition, change from baseline to worst post-baseline assessment in suicidality categories will be summarized by treatment group.

5.7 OTHER ANALYSES

5.7.1 Summaries of Conduct of Study

The summary of study conduct will include a description of the following items by treatment arm:

- Number of participants enrolled and randomized
- Number of participants included in each analysis set
- Number and percentage of participants who prematurely withdrew from the study or from study treatment (including the reasons for discontinuation and the distribution of these discontinuations by time-windowed visit)
- Incidence of protocol deviations – overall and by four main categories (inclusion criteria, exclusion criteria, medication and procedural)
- Stratification factor reported in IxRS and used for randomization
- Number of participants with home nursing
- Number of participants initiating or changing symptomatic treatment of AD during the study

Major protocol deviations and premature withdrawals will be listed.

5.7.2 Summaries of Treatment Group Comparability

Demographics and baseline characteristics (including age, sex, medical history, randomization stratification factors) will be summarized descriptively by treatment arm as assigned for the ITT analysis set using:

- means, SDs, medians, and ranges for continuous variables
- counts and proportions for categorical variables

Exposure to AD concomitant medication (including post-baseline initiation or change in dose) will be summarized by treatment arm for the ITT analysis set.

5.7.3 Immunogenicity Analyses

Immunogenicity analyses include the evaluation for antibodies against gantenerumab, including the determination of antibody titers. The results of the confirmatory assay will be presented as a frequency table summarizing baseline and post-baseline results.

A listing of participants with positive ADA status per confirmatory assay and titer result will be provided.

5.7.4 Summaries of COVID-19 Impact on the Trials

Studies GRADUATE I and GRADUATE II were ongoing during the COVID-19 pandemic. Consequently, to monitor the potential impact of the pandemic on the trials, we will provide a specific set of descriptive analyses related to COVID-19 by treatment arm for the ITT analysis set (see Table 2), including:

- Demographic and Baseline Characteristics in Participants with Confirmed/Suspected COVID-19
- COVID-19 AEs (see Section 5.6.2)
- COVID-19 related Protocol Deviations
- Missed doses due to COVID-19
- Study discontinuations due to COVID-19 as determined by the adjudication committee for ICEs
- Study drug administrations of 1020 mg Q4W
- Remote scale administrations
- Duration of study site closure

5.7.5 Amyloid PET Substudy

The objective of the GRADUATE I and GRADUATE II longitudinal amyloid PET substudies is to assess changes in brain amyloid load over time using the change in florbetaben or flutemetamol from baseline to the last amyloid PET visit in the Standard Uptake Value Ratio (SUVR).

Two amyloid PET ligands are allowed in the GRADUATE I and GRADUATE II longitudinal amyloid PET substudies to provide assessment of β-amyloid protein deposition according to country and site availability: radiopharmaceuticals florbetaben-F18 and flutemetamol-F18. However, the same ligand has to be used for the same participant throughout the study (e.g., if a participant has been enrolled in the main study with a positive florbetaben PET scan, only florbetaben will be allowed and used for the longitudinal follow-up scans for the participant).

Centiloid mapping will be completed for SUVR data from the two amyloid PET ligands. The primary amyloid PET outcome measure is the change in amyloid PET Centiloid from baseline to Week 116.

5.7.5.1 General considerations on Amyloid PET statistical analyses

With the Centiloid endpoint, data from both tracers will be pooled and analyzed together. Separate analysis by tracer with the Centiloid endpoint may also be conducted as appropriate. When SUVR metrics is the endpoint, the analysis will be done separately and reported separately for each tracer, when possible.

Missing values will not be imputed.

The amyloid PET analyses will be performed on the Amyloid-PET-mITT analysis set (see Table 2), unless otherwise specified, and participants will be analyzed according to the treatment assigned at randomization by IxRS.

5.7.5.2 Summaries of Treatment Group Comparability

Demographics and baseline characteristics (including age, sex, medical history, randomization stratification factors) will be summarized descriptively by treatment arm as assigned for both the Amyloid-PET-mITT analysis set and the Amyloid-PET-longitudinal analysis set (see Table 2) using:

- means, SDs, medians, and ranges for continuous variables
- counts and proportions for categorical variables

5.7.5.3 Visit Windowing

For amyloid PET assessments, due to the long time between scheduled assessments, time windows based on study days, as defined in Table 7, will be used. Study days are defined based on days on study since the date of the first dose, with the day of the first dose being study day 1.

Table 7 Time Windows for Amyloid PET Assessments

Visit	Target day	Time window
Baseline	1	Up to day 35
Week 52	365	281, 449
Week 116	813	645, 897

For Week 116, the time window will cover the week 104 timepoint as well. In case of more than one assessment within a time window, the assessment with the date closest to the target day is selected. For the combined window of Week 104 and 116, the target day is the Week 116 assessment day.

Because of visit windowing, data collected at an early termination visit will be summarized at the corresponding visit as defined by the time window. For participants who have discontinued treatment early, if a PET scan is performed more than 56 days (early termination visit expected 14 days after last dose, followed by time window per protocol for early termination is ±42 days) after the date of last dose, the PET scan will not be used for the analysis.

The end of a substudy is defined as the date when all participants enrolled in the substudy have:

1. completed the last required amyloid PET scan (Week 116), or
2. completed an early termination scan, or
3. discontinued from the main study.

5.7.5.4 Definition of the Estimand for Amyloid PET

The scientific question of interest for the amyloid PET substudies is to assess the effect of the intended study treatment on the PD endpoint, change from baseline in amyloid load burden at Week 116, in the absence of a substantial impact of the COVID-19 pandemic and as if treatment discontinuation would not have occurred.

The primary Amyloid PET estimand is thus described by the following attributes:

- **Target Population**:
  Early (prodromal to mild) AD population as identified by the inclusion and exclusion criteria, see Sections 4.1.1 and 4.1.2 of the substudy protocols and Sections 4.1.1 and 4.1.2 of the main study protocols
- **Variable**:
  Change from baseline to Week 116 in amyloid PET Centiloid
- **Treatment**:
  Prescribed study drug including up-titration to the target dose
- **Population-level summary**:
  Difference in variable means between treatment arms
- Intercurrent events
  - Substantial reduction in drug exposure due to the COVID-19 pandemic (defined as $\geq$4 missed dose-months)
  - Treatment discontinuation due to any reason

Amyloid PET is listed in the protocol under “Pharmacodynamic Biomarker Objective”. Considering that Amyloid PET primarily aims at estimating the Pharmacodynamic effect of the drug, rather than a direct measure of clinical efficacy, reporting treatment effect estimated "as if there were no treatment discontinuations and no substantial reduction in exposure due to COVID-19 pandemic" (thus using a hypothetical strategy) addresses the scientific question of interest.

Details for Definition of Variable

The Centiloid variable will be used rather than the original SUVR, because it allows to combine data from different tracers, by mapping SUVR values to a standardized scale. The Centiloid variable is the current common standard in the scientific community.

The primary SUVR measure of interest is computed using a weighted composite target region and whole cerebellum as reference region. The weighted composite target region is composed of (both left and right side):

- frontal lobe,
- parietal lobe,
- temporal lobe lateral,

- cingulum posterior and
- anterior cingulate gyrus

Each region is weighted by its own volume. The Centiloid conversion is a linear transformation of SUVR with tracer-specific parameters that are given below:

Centiloid Equation:

$$CL = SlopeCL \times SUVR + InterceptCL$$

CL = Centiloids; SlopeCL = slope; SUVR = standard uptake value ratio of the target region; InterceptCL = intercept.

The pertinent values for the two tracers are:

Table 8 Primary Centiloid Equation Parameters

Tracer	Reference	Slope	Intercept
Florbetaben-F18	whole cerebellum	175.6	-174.2
Flutemetamol-F18	whole cerebellum	143.5	-141.1

5.7.5.5 Main Analytical Approach

An MMRM will be used to estimate the mean change in Centiloid from baseline to Week 116 within each of the substudies. The model will include the change from baseline in Centiloids as the dependent variable, while adjusting for treatment arm (as categorical), visit (as categorical), APOE ε4 status (as categorical; carrier vs non-carrier), type of tracer (as categorical; Florbetaben vs Flutemetamol), baseline Centiloid, baseline Centiloid-by-visit and treatment-by-visit interaction. Visit will be treated as the repeated variable within a participant. An unstructured variance-covariance matrix will be applied to model the within-participant errors; in the case of non-convergence, compound symmetry will be used, together with a robust estimator of standard error ("sandwich" estimator).

In line with the estimand definition, data acquired after the ICE "Substantial reduction in drug exposure due to the COVID-19 pandemic" (as defined in Table 3) or more than 56 days from treatment discontinuation will be excluded from the analysis and treated as missing for the primary analysis purposes.

There will be no data imputation for missing data. However, the MMRM provides unbiased estimates and valid inference in the presence of missing data, under the MAR (missing at random) assumption.

The difference in least squares means between active drug and placebo arms at Week 116 will be estimated and presented alongside p-value and the 95% confidence interval for treatment difference. A p-value <0.0001 will be regarded as a statistically significant evidence, irrespective of the results of the other primary/secondary endpoints

(along the lines of the Haybittle–Peto rule, and thus maintaining the overall type-I error within the study).

5.7.5.6 Supplementary analyses

Changes in weighted Composite Summary region SUVR (for each tracer) and Centiloids from baseline will be summarized using descriptive statistics.

Based on the same model as specified in the Section 5.7.5.4, the change from baseline to Week 52 in Centiloids will also be reported as supplementary analysis.

Additionally, the number and proportion of participants with values below or equal to the positivity threshold will be summarized for each assessment time point. Centiloid zero is the mean amyloid burden for a typical population of young healthy controls, and 100 Centiloid is the typical mean of a population with AD. The Centiloid value of 24 is consistent with the diagnostic amyloid positivity threshold (Klunk et al. 2015; Navitsky et al. 2018) (see Section 5.7.5.3 for definition of Centiloid).

A chi-square test (or Fisher's exact test, whichever is appropriate) will be used to compare the proportions of participants with values below or up to the positivity threshold between the active drug and placebo arm.

In order to account for the potential impact of missing values, a completers analysis will be performed, i.e., restricting the analysis to participants who completed the visit with non-missing data.

5.7.6 Tau PET Substudy

There is a single tau PET substudy enrolling subjects from both studies (WN29922/WN39658 Longitudinal Tau PET Substudy). This substudy utilizes [^{18}F]GTP1 (RO6880276) as tau PET radioligand.

Statistical analyses will be conducted on tau PET Median Standardized Uptake Value Ratios (SUVR) in the following four target regions of interest. In composite target regions, each region is weighted by its own volume.

- A temporal composite target region. This region is composed of (both left and right):
    - anterior and posterior superior temporal gyrus,
    - posterior temporal lobe,
    - fusiform gyrus,
    - middle and inferior temporal gyrus;

- A medial temporal composite region not including the hippocampus, composed of (both left and right):
    - Amygdala,
    - Parahippocampus,
    - Anterior medial and lateral temporal lobe;
- Frontal lobe (both left and right);
- Parietal lobe (both left and right);

The inferior cerebellar grey matter will be used as reference region for the calculation of median SUVRs for all four target regions considered.

All the statistical analyses will be based on the Tau-PET-mITT analysis set (see Table 2) unless otherwise specified.

5.7.6.1 Summaries of Treatment Group Comparability

Demographics and baseline characteristics (including age, sex, medical history, randomization stratification factors) will be summarized descriptively by treatment arm as assigned for both the Tau-PET-mITT analysis set and the Tau-PET-longitudinal analysis set (see Table 2) using:

- means, SDs, medians, and ranges for continuous variables
- counts and proportions for categorical variables

5.7.6.2 Definition of the Estimand

The scientific question of interest for the Tau PET substudy is to assess the effect of the intended study treatment on the PD endpoint, change from baseline in tau PET median SUVR at Week 116, in the absence of a substantial impact of the COVID-19 pandemic and as if treatment discontinuation would not have occurred. The same estimand will be considered for all four median SUVRs regions.

The primary Tau PET estimand is thus described by the following attributes:

- **Target Population**:
  Early (prodromal to mild) AD population as identified by the inclusion and exclusion criteria, see Sections 4.1.1 and 4.1.2 of the substudy protocols and Sections 4.1.1 and 4.1.2 of the main study protocols
- **Variable**:
  Change from baseline to Week 116 in tau PET median SUVR
- **Treatment**:
  Prescribed study drug including up-titration to the target dose
- **Population-level summary**:
  Difference in variable means between treatment arms
- Intercurrent events

- Substantial reduction in drug exposure due to the COVID-19 pandemic (defined as ≥4 missed dose-months)
- Treatment discontinuation due to any reason

Tau PET is listed in the protocol under “Pharmacodynamic Biomarker Objective”. Considering that tau PET aims at estimating the Pharmacodynamic effect of treatment, reporting treatment effect estimated "as if there were no treatment discontinuations and no substantial reduction in exposure due to COVID-19 pandemic" (thus using an hypothetical strategy) addresses the scientific question of interest.

Since there are not individual Tau PET substudies for GRADUATE I and GRADUATE II, but rather a single Tau PET substudy across all patients from GRADUATE I and GRADUATE II, Tau PET will be analyzed at the pooled level of GRADUATE I and GRADUATE II.

5.7.6.3 Main Analytical Approach

An MMRM analysis will be used to estimate the mean change from baseline to Week 116 for each of the median SUVRs defined. The model will include the change from baseline in median SUVR as the dependent variable, while adjusting for treatment arm (as categorical), visit (as categorical), APOE ε4 status (as categorical; carrier vs non-carrier), baseline median SUVR, baseline median SUVR-by-visit, study, study-by-visit and treatment-by-visit interaction. Visit will be treated as the repeated variable within a participant. An unstructured variance-covariance matrix will be applied to model the within-participant errors; in the case of non-convergence, compound symmetry will be used, together with a robust estimator of standard error (“sandwich” estimator).

In line with the estimand definition, data acquired after the ICE “Substantial reduction in drug exposure due to the COVID-19 pandemic” (as defined in Table 3) or more than 56 days from last dose will be excluded from the analysis and treated as missing for the primary analysis purposes.

There will be no data imputation for missing data. However, the MMRM provides unbiased estimates and valid inference in the presence of missing data, under the MAR (missing at random) assumption. A subgroup analysis by parent study may be also considered in order to derive a study-specific treatment effect.

Based the same MMRM model already described in this section, the change from baseline to week 52 in tau PET will also be reported as supplementary analysis.

5.7.6.4 Visit Windowing

For tau PET assessments, due to the long time between scheduled assessments, time windows based on study days, as defined in Table 9, will be used. Study days are

defined based on days on study since the date of the first dose, with the day of the first dose being Study Day 1.

Table 9 Time Windows for tau PET Assessments

Visit	Target study day	Time window
Baseline	1	Up to day 35
Week 52	365	281, 449
Week 116	813	645, 897

5.7.7 Cerebrospinal Fluid (CSF) Analyses

The main analysis for the CSF biomarkers will be based on the pooled dataset of GRADUATE I and GRADUATE II studies (due to the small number of CSF samples within each study). Analyses at individual study level will be conducted as well.

Analysis of CSF biomarkers will be based on the CSF-mITT analysis set unless otherwise specified.

CSF biomarker data will be summarized by treatment group and visit (see schedule of assessment in the study protocol).

An ANCOVA analysis will be used to estimate the mean change from baseline to Week 116 for each CSF biomarker. The model will include the change from baseline in the CSF biomarker as the dependent variable, while adjusting for treatment arm (as categorical), study, APOE ε4 status (as categorical; carrier vs non-carrier) and baseline biomarker level. The ANCOVA model will be based on log-transformed biomarker data.

There will be no data imputation for missing data.

The following CSF biomarkers will be analyzed:

- Total tau (tTau)
- Phosphorylated tau (pTau-181)
- Neurogranin
- Neurofilament light (NFL)

Other exploratory CSF biomarker may be reported separately.

Summaries of Treatment Group Comparability

Demographics and baseline characteristics (including age, sex, medical history, randomization stratification factors) will be summarized descriptively by treatment arm as assigned for both the CSF-mITT analysis set and the CSF-longitudinal analysis set (see Table 2) using:

- means, SDs, medians, and ranges for continuous variables
- counts and proportions for categorical variables

Visit Windowing

For CSF assessments time windows based on study days, as defined in Table 10, will be used. Study days are defined based on days on study since the date of the first dose, with the day of the first dose being Study Day 1.

Table 10 Time Windows for CSF Assessments

Visit	Target study day	Time window
Baseline	1	Up to day 35
Week 116	813	645, 897

5.7.8 Plasma Biomarker Analyses

Plasma biomarkers will be analyzed separately for each study (GRADUATE I and GRADUATE II).

Analysis of plasma biomarkers will be based on the ITT analysis set unless otherwise specified.

The plasma biomarkers will be summarized by treatment group and visit (see schedule of assessment in the study protocol).

An MMRM analysis will be used to estimate the mean change from baseline to Week 116 (but also to Week 24, 52 and 104) for each plasma biomarker. The model will include the change from baseline in the plasma biomarker as the dependent variable, while adjusting for treatment arm (as categorical), visit (as categorical), treatment-by-visit interaction, APOE ε4 status (as categorical; carrier vs non-carrier), baseline biomarker and baseline biomarker-by-visit. Visit will be treated as the repeated variable within a participant. An unstructured variance-covariance matrix will be applied to model the within-participant errors; in case of non-convergence, compound symmetry will be used, together with a robust estimator of standard error (“sandwich” estimator). The MMRM model will be based on log-transformed biomarker data.

There will be no data imputation for missing data. However, the MMRM provides unbiased estimates and valid inference in the presence of missing data, under the MAR (missing at random) assumption.

The following plasma biomarkers will be analyzed:

- Amyloid beta (1-42) (Abeta-42)
- Phosphorylated tau (pTau-181)

Other exploratory plasma biomarkers may be reported separately.

Summaries of Treatment Group Comparability

Demographics and baseline characteristics (including age, sex, medical history, randomization stratification factors) will be summarized descriptively by treatment arm as assigned for both the ITT analysis set and the Plasma-longitudinal analysis set (see Table 2) using:

- means, SDs, medians, and ranges for continuous variables
- counts and proportions for categorical variables

Visit Windowing

For Plasma assessments time windows based on study days, as defined in Table 11, will be used. Study days are defined based on days on study since the date of the first dose, with the day of the first dose being Study Day 1.

Table 11 Time windows for Plasma assessments

Visit	Target study day	Time window
Baseline	1	Up to Day 35
Week 24	169	85, 253
Week 52	365	281, 449
Week 104	729	645, 770
Week 116	813	771, 897

5.7.9 Volumetric MRI Analyses

Structural MRI will be analyzed separately for each study (GRADUATE I and GRADUATE II).

Analysis of structural MRI (volumetric MRI) will be based on the MRI-mITT analysis set unless otherwise specified.

Volumetric MRI, for each brain region, will be summarized by treatment group and visit using descriptive statistics for the absolute volume at baseline and percent change from baseline at post-baseline visits.

An MMRM analysis will be used to estimate the mean percent change from baseline to Week 116 (as well Week 48 and 104) in Volumetric MRI for each brain region. The model will include the percent change from baseline in volumetric MRI as the dependent variable, while adjusting for treatment arm (as categorical), visit (as categorical), treatment-by-visit interaction, baseline age, gender (as categorical), APOE ε4 status (as categorical; carrier vs. non-carrier) and disease stage (as categorical). Visit will be treated as the repeated variable within a participant. An unstructured variance-covariance matrix will be applied to model the within-participant errors; in the case of non-convergence, compound symmetry will be used, together with a robust estimator of standard error ("sandwich" estimator).

There will be no data imputation for missing data. However, the MMRM provides unbiased estimates and valid inference in the presence of missing data, under the MAR (missing at random) assumption.

The following brain regions will be considered:

- Whole brain
- Ventricles
- Hippocampus right and left
- Cortical gray matter

Other exploratory analyses based on other brain regions may be reported separately.

Summaries of Treatment Group Comparability

Demographics and baseline characteristics (including age, sex, medical history, randomization stratification factors) will be summarized descriptively by treatment arm as assigned for both the MRI-mITT analysis set and the MRI-longitudinal analysis set (see Table 2) using:

- means, SDs, medians, and ranges for continuous variables
- counts and proportions for categorical variables

Visit Windowing

For Volumetric MRI assessments time windows based on study days, as defined in Table 12, will be used. Study days are defined based on days on study since the date of the first dose, with the day of the first dose being Study Day 1.

Table 12 Time windows for Volumetric MRI assessments

Visit	Target study day	Time window
Baseline	1	Up to Day 35
Week 48	337	253, 421
Week 104	729	645, 770
Week 116	813	771, 897

5.8 INTERIM ANALYSES

Details of interim analysis plans are described in a separate interim analysis SAP (iSAP), providing information about a futility interim analysis based on the primary efficacy endpoint CDR-SB.

Other than the futility analysis, there is no plan for an efficacy interim analysis based on the primary endpoint. The primary analysis of the clinical efficacy endpoints will be performed only once, after completion of the efficacy data collection at the end of the double blind part of the study (as described in this SAP) and it will be the only opportunity to formally reject the primary null hypothesis of the trial.

6. SUPPORTING DOCUMENTATION

This document is part of a broader Data Analysis Plan that has several documents, including:

- Graduates studies interim analysis SAP
- Graduates studies Data Analysis Plan Module 2
- Graduates studies Data Analysis Plan Module 3

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Appendix 1 Type I Error Control Considerations for Reference-Based Conditional Mean Imputation Combined with the Jackknife for Inference

Introduction

In the GRADUATE trials, hypothetical and treatment policy strategies are applied to Non Study Drug or Condition Related (NSDCR) intercurrent events (ICEs) and Study Drug or Condition Related (SDCR) ICEs, respectively That is, the clinical interest is in a scenario where SDCR ICEs but not NSDCR ICEs do occur. For estimating the treatment effect, data after NSDCR are assumed to missing at random (MAR) whereas missing data after SDCR are imputed based on the placebo group in both treatment groups using the copy-increments-in-reference (CIR) imputation method, a specific type of reference-based imputation. We refer to Section 5.3.3 for further details.

The primary analysis of the GRADUATE trials is implemented using conditional mean imputation of missing data combined with the jackknife for inference. This methodology has been described and justified in Wolbers et al. (2022). In this appendix, we provide further details regarding type I error control of the method including additional simulations targeted to the setting of the GRADUATE trials.

Theoretical and published simulation evidence for type I error control

As demonstrated in Section 2.5 of Wolbers et al. (2022), the proposed conditional mean imputation methodology corresponds to a computationally efficient implementation of maximum likelihood multiple imputation. Estimators based on maximum likelihood imputation are asymptotically normal and unbiased if the imputation model and the associated missing data assumptions are correctly specified (Wang and Robins (1998), Robins and Wang [2000]). Moreover, standard error estimates based on resampling methods such as the jackknife or the bootstrap are consistent (Bartlett and Hughes (2020), von Hippel and Bartlett (2021), Wolbers et al. (2022).

Therefore, large-sample (asymptotic) type I error control is guaranteed if the imputation model and the associated missing data assumptions are correctly specified. This is the case if the following conditions hold:

- All ICEs are correctly identified and classified as NSDCR or SDCR.
- Observed outcome data prior to an ICEs follow a multivariate normal mixed model for repeated measures (MMRM) with an unstructured covariance matrix.
- Missing outcome data prior to an ICE are missing at random (MAR).
- Missing outcome data after NSDCR ICEs compatible with a hypothetical strategy is also MAR.
- Missing outcome data after SDCR ICEs are compatible with the copy-increments-in-reference (CIR) assumption.

In contrast, the commonly used MMRM model requires that all missing data are MAR (Mallinckrodt et al. [2008]). In many settings, a reference-based missing data assumption for SDCR ICEs such as CIR is arguably more plausible and conservative than the MAR assumption of the classical MMRM model.

In order to study type I error control for finite sample sizes, simulation studies are required. A simulation study reported in Wolbers et al. (2022) assessed type I error via simulation (based on 100,000 simulations) for a setting with a relatively low sample size (100 subjects per group), a large proportion of ICEs (34% and 24% in the active and placebo groups, respectively), and a large probability of study drop-out after the occurrence of the ICE of 75%. For standard MAR and all reference-based imputation methods, inference based on conditional mean imputation and jackknifing strictly protected type I error. Simulation results reported in Liu and Pang (2016) for a similar method also found no evidence of type I error inflation for reference-based methods or the MMRM model if the missing date mechanism was correctly specified. These simulation results are also consistent with simulation studies which report that the MMRM model (or an asymptotically equivalent multiple imputation model) provides adequate type I error control if all missing data are MAR (Siddiqui [2011], Lu and Mehrotra [2010]).

In contrast, statistical methods cannot be expected to strictly control type I error if the missing data assumptions are not correctly specified. For example, simulations reported in Liu and Pang (2016) demonstrate type I error inflation for both reference-based methods and the MMRM model if missing data are simulated under certain missing not at random (MNAR) scenarios. Similarly, Mallinckrodt et al. (2004) demonstrated type I inflation of the MMRM model under MNAR scenarios but type I error control of the MMRM model was much closer to nominal values compared to naive approaches to missing data such as the last observation carried forward (LOCF) approach. Whether or not the missing data assumptions is correctly specified is by nature something that cannot be verified

In conclusion, reference-based imputation methods based on conditional mean imputation and jackknifing control type I error if the imputation model and the associated missing data assumptions are correctly specified. Neither reference-based imputation methods nor the MMRM model can guarantee strict type I error control if the missing data assumptions are not correctly specified. Therefore, sensitivity analyses such as tipping point analyses should always be performed to assess the robustness of the results to deviations from the missing data assumptions.

Additional Simulations Targeted to the Setting of the GRADUATE Trials

Methods

We conducted a simulation study to further investigate the type I error control of the reference-based conditional mean imputation combined with the jackknife for inference. The set-up of the simulation study is similar to the simulations reported in Wolbers et al. (2022), but the simulation parameters and the scenarios considered are adapted to the GRADUATE trials. All simulations were for 1:1 randomized placebo-controlled trials with 508 subjects per group and visits at baseline and at 24, 52, 76, 104, and 116 weeks of follow-up. All simulations were performed under the null hypothesis of no difference in mean outcome trajectories between the groups. Scenarios including different probabilities of ICEs in the two groups and/or misclassification of SDCR ICEs as NSDCR ICEs were also included as described below.

Specifically, the other simulation parameters were chosen as follows:

- The mean outcome trajectory in both groups increased linearly from 3.65 to 4.65 during the first 52 weeks from baseline (i.e., an increase of 1 point in the first year), and increased linearly by 1.5 points per year afterwards.
- The variances of the outcomes at baseline and follow-up visits in both groups were: 1.53, 2.08, 2.65, 3.19, 4.26, 4.26.
- The correlation matrix of the baseline and follow-up values in both groups is shown on Table 1.

Table 1 Correlation Matrix

	Baseline	Week 24	Week 52	Week 76	Week 104	Week 116
Baseline	1	0.72	0.60	0.54	0.52	0.52
Week 24	0.72	1	0.72	0.60	0.54	0.54
Week 52	0.60	0.72	1	0.72	0.60	0.60
Week 76	0.54	0.60	0.72	1	0.72	0.72
Week 104	0.52	0.54	0.60	0.72	1	0.85
Week 116	0.52	0.54	0.60	0.72	0.85	1

- Two types of intercurrent events were simulated: Study Drug or Condition Related ICEs (SDCR) and Non-Study Drug or Condition Related ICEs (NSDCR).
- Simulation of SDCR ICEs:
  - The probability of an SDCR ICE after each visit was calculated according to a logistic model, which also depended on the observed outcome at that visit.
  - The visit-wise probability of an SDCR ICE for a subject with an observed outcome at that visit of 3.65 was varied across 4 different scenarios as reported in Table 2.
  - The odds of an SDCR ICE further increased by 45% for each 1 point increase in the observed outcome.
  - In the placebo group, an SDCR ICE had no effect on the mean trajectory. In the active group, subjects who experienced an SDCR ICE followed the slope of the mean trajectory from the placebo group from that time point onward (CIR).
  - Study drop-out after the SDCR ICE visit occurred with a probability of 80% leading to missing outcome data from that time point onward.
- Simulation of NSDCR ICEs:
  - The probability of an NSDCR ICEs after each visit was assumed to be independent of the visit and the observed outcome. The specification of these probabilities for each of the 4 scenarios is presented in Table 2.
  - NSDCR ICEs always led to missing outcome data from that time point onward.
- If both SDCR and NSDCR ICEs were simulated to occur for a subject, then it was assumed that only the earlier of them counted. In case both ICEs were simulated to occur at the same time, the event was considered a SDCR ICE. This means that a single subject could experience either a SDCR or a NSDCR ICE, but not both of them.
- Additional missing data unassociated with an ICE was simulated by assuming that a subject missed any visit with a probability of 5%.

Table 2 Specifications of ICEs Probabilities in Each Group for the Four Simulation Scenarios. Only the Parameters that Varied Across Different Scenarios are Presented in this Table.

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Probability of a SDCR ICE after each visit for a subject with outcome equal to 3.65 (PLACEBO)	2%	1.5%	3%	2.5%
Probability of a SDCR ICE after each visit for a subject with outcome equal to 3.65 (ACTIVE)	2%	2.5%	3%	3.5%
Probability of a NSDCR ICE after each visit (PLACEBO)	2.5%	2%	0%	0%
Probability of a NSDCR ICE after each visit (ACTIVE)	2.5%	3%	0%	0%

Scenario 1 specifies equal ICE probabilities for the two groups, while Scenario 2 specifies a higher probability of both SDCR and NSDCR events in the active group compared to the placebo group. Scenario 3 simulates only SDCR events, with equal probabilities across the two groups. Scenario 4 also simulates only SDCR events, but with a higher probability in the active group.

Results

The overall probability for a subject to experience either a SDCR or a NSDCR event during the trial under the four scenarios is reported in Table 3. These probabilities were estimated via simulation of a large trial with a sample size of 100'000 subjects per group.

Table 3 Overall Probability for a Subject to Experience Either a SDCR or a NSDCR Event during the Trial under all the Scenarios Considered. Probabilities were Estimated via Simulation of a Large Trial with a Sample Size of 100'000 Subjects Per Group.

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Probability of SDCR ICE (PLACEBO)	21%	17%	30%	27%
Probability of SDCR ICE (ACTIVE)	21%	24%	30%	33%
Probability of NSDCR ICE (PLACEBO)	11%	9%	0%	0%
Probability of NSDCR ICE (ACTIVE)	11%	12%	0%	0%
Overall ICE probability (PLACEBO)	32%	26%	30%	27%
Overall ICE probability (ACTIVE)	32%	36%	30%	33%

For each scenario considered, we assumed that a given fraction of SDCR ICEs had been misclassified as NSDCR ICEs. That is, we will apply a hypothetical strategy not only to those ICEs that are truly NSDCR, but also to a given fraction of SDCR events. The misclassification rate varied as follows: 0%, 15%, 30%, 45%, where 0% means that there is no misclassification of any SDCR event, while 45% means that 45% of SDCR events will be classified (and handled) as NSDCR events.

Type I error was simulated based on 10'000 simulated trials for each scenario. The respective misclassification rates were then applied to these data before the analysis. The analysis was consistent with the primary analysis of the GRADUATE trial, i.e., conditional mean imputation with jackknife-based inference (as described in Wolbers et al. [2022]) with copy-increments-in-reference (CIR) imputation for missing data after SDCR ICEs.

The simulation results are summarized in Table 4. Simulated type I errors ranged from 4.69% to 5.18% across scenarios and misclassification rates. Simulations based on 10,000 simulated data sets provide a Monte Carlo standard error for type I error estimates of approximately $\pm 0.22\%$. Therefore, these results are fully consistent with strict type I error control at the 5% significance level.

Table 4 Type I Error Rate Estimates for Each of the Scenarios and Misclassification Rates. Simulations are based on 10,000 Simulated Data Sets which Provide a Monte Carlo Standard Error for Type I Error Estimates of Approximately 0.22%.

Scenario	ICE misclassification rate (from SDCR to NSDCR)	Type I error
Scenario 1	0%	4.95%
	15%	4.84%
	30%	4.97%
	45%	4.83%
Scenario 2	0%	5.11%
	15%	5.00%
	30%	5.18%
	45%	5.13%
Scenario 3	0%	4.98%
	15%	4.81%
	30%	4.82%
	45%	4.69%
Scenario 4	0%	4.73%
	15%	4.78%
	30%	5.00%
	45%	5.01%

Conclusion

The primary analysis described in this SAP is based on the method described in Wolbers et al. (2022). This publication describes and justifies the method in detail and provides theoretical and simulation support that it controls type I error.

Clarification and details on the theoretical argument were provided and additional simulations were conducted. These simulations explored plausible scenarios calibrated to the GRADUATE studies. They also assessed the impact of ICE misclassification.

Based on this body of evidence, the proposed method for primary analysis (using conditional mean imputation of missing data combined with the jackknife for inference) adequately controls type I error.

Appendix 2 ADCS-ADL Dependence Scale Algorithm Version 2.1

Item Domains Used in the Algorithm

- bADL - basic Activities of Daily Living: Questions 1-5, 6B
- iADL – instrumental Activities of Daily Living
  - Household Activities: Questions 6A, 7, 10-14, 23
  - Communication and Engagement: Questions 17, 21, 22
  - Outside Activities: Questions 15, 16A, 16B, 18

Note that 4 items included in the original communication and engagement algorithm are not included in the updated algorithm. Specifically concentrating on a television programme (Q8), participating in small talk (Q9), talking about current events (Q19), recalling information recently read in book/magazine (Q20) were excluded. Whilst these concepts are clearly important to quality of life, they do not require supervision and are therefore not considered fundamental to independence.

The algorithm starts by checking the requirements for Level 5 which is the highest level of impairment and continues to check each lower level until the patient meets the requirements of a level and is assigned to that level. If a patient does not meet the requirements for any of Levels 1-5, then the patient is assigned Level 0.

- **Level 0:** is the dependence level assigned when a patient has no recorded impairment
- **Level 1**: Item score $=2$ on one or more items from only one of the following clusters: Household Activities, Communication and Engagement, Outside Activities. There should be no bADL impairment.
- **Level 2:** Item Score $=2$ on one or more items from two or more of the following clusters: Household Activities, Communication and Engagement, Outside Activities, OR Item Score ≤ 1 on one or more items from any of the following clusters: Household Activities, Communication and Engagement. (There should be no bADL impairment).
- **Level 3:** Item Score ≤ 2 for all items from the following clusters: Household Activities, Communication and Engagement, Outside Activities, OR Item Score ≤ 1 on one or more items from Outside Activities, OR Item Score $=2$ for Bathing (Q4), Score $=2$ for toileting (Q3), Score $=3$ for dressing, score $=1$ or 2 for eating OR Item score $=2$ for walking
- **Level 4**: Any one of the following: Item Score ≤ 2 for Grooming (Q5), Item score ≤ 1 for Bathing (Q4) item score $=1$ for toileting (Q3) or Item score ≤ 2 for dressing, OR item score $=0$ for Eating (Q1) or Item score $=1$ for walking
- **Level 5**: Item Score $=0$ for either Walking (Q2) or Toileting (Q3)

Item recoding in preparation for application of the algorithm

Item 16B with a binary response (0/1) was recoded to 0/3 so that the “no impairment” level was consistent across items.

Item 21 was recoded such that a score of 2 (ability to write short notes or messages that others understood) would not be considered “impaired” for the purposes of the dependence scale and was collapsed with response option 3 (letters or long notes that others understood). This was achieved by recoding 2 to 3.

Missing data was not imputed. “Don’t know” responses were also treated as missing and not imputed. The dependence scale score was not scored if there were more than 2 missing items and/or any of the bADL items were missing.

Appendix 3 Charter for Adjudication Committee for Intercurrent Events

CHARTER FOR ADJUDICATION COMMITTEE FOR INTERCURRENT EVENTS

TITLE:	**TWO PHASE III, MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY, AND SAFETY STUDIES OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**
PROTOCOLS:	WN29922, WN39658
AUTHOR:	[redacted]
IND NUMBERS:	102,266
EUDRACT NUMBERS:	2017-001364-38 (Study WN29922) 2017-001365-24 (Study WN39658)
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	01 September 2021

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1. VERSION HISTORY

Version	Date	Details
Version 1	01September2021	Creation

ADJUDICATION COMMITTEE FOR INTERCURRENT EVENTS MEMBER SIGNATURES

TITLE: **TWO PHASE III, MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY, AND SAFETY STUDIES OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**

PROTOCOLS: WN29922
WN39658

I have read this Charter and confirm that, to the best of my knowledge, it accurately describes the conduct of the Adjudication Committee for Intercurrent Events.

DocuSigned by:
[redacted]
B97097216CF14A1...

[redacted], MD
[redacted],
F. Hoffmann-La Roche Ltd
([redacted])

Date 9/1/2021

ADJUDICATION COMMITTEE FOR INTERCURRENT EVENTS MEMBER SIGNATURES

TITLE: **TWO PHASE III, MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY, AND SAFETY STUDIES OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**

PROTOCOLS: WN29922
WN39658

I have read this Charter and confirm that, to the best of my knowledge, it accurately describes the conduct of the Adjudication Committee for Intercurrent Events.

DocuSigned by:
[redacted]
C73603349D0D4C4...

[redacted]
F. Hoffmann-La Roche Ltd

Date 9/2/2021

ADJUDICATION COMMITTEE FOR INTERCURRENT EVENTS MEMBER SIGNATURES

TITLE: **TWO PHASE III, MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY, AND SAFETY STUDIES OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**

PROTOCOLS: WN29922
WN39658

I have read this Charter and confirm that, to the best of my knowledge, it accurately describes the conduct of the Adjudication Committee for Intercurrent Events.

DocuSigned by:
[redacted]
538E17B187EB44B...

[redacted]
F. Hoffmann-La Roche Ltd

Date 9/2/2021

2. INTRODUCTION

RO4909832 (gantenerumab) is a fully human monoclonal antibody targeting aggregated forms of amyloid-β including oligomers, fibrils, and plaques. Studies WN29922 and WN39658, defined as GRADUATE studies, will evaluate the efficacy and safety of gantenerumab compared with placebo for the treatment of patients with early (prodromal to mild) Alzheimer's disease.

Intercurrent events (ICEs) are defined as events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. In order to estimate precisely the treatment effect as described as the primary estimand, it is crucial to correctly identify and address these ICEs. ICEs will either be considered Non Study Drug or Condition Related (NSDCR) or Study Drug or Condition Related (SDCR). For the primary estimand of the GRADUATE studies, the Sponsor is proposing a treatment policy approach for all SDCR ICEs. All remaining NSDCR ICEs will be handled using a hypothetical approach.

This Charter contains a description of the adjudication committee for intercurrent events (ACI) membership and operations for Studies WN29922 and WN39658. The ACI will review the ICEs related to study treatment discontinuation where ambiguity exists in order to support the study team classifying them as NSDCR or SDCR as per the SAP.

Terms and abbreviations used in this Charter are defined in Table 1.

Table 1 Terms and Abbreviations

Term and Abbreviation	Definition
ACI	Adjudication committee for intercurrent events
eCRF	electronic Case Report Form
ICEs	Intercurrent events
NSDCR	Non Study Drug or Condition Related
SDCR	Study Drug or Condition Related
Sponsor	F. Hoffmann-La Roche Ltd
Study Team	Team composed of Sponsor employees directly involved with the study leadership team (SLT)
unblinding data	data for which treatment assignment is identified

3. ROLE OF THE COMMITTEE

The Study Team delegates to the ACI the responsibility to review and sort ICEs as SDCR or NSDCR according to prespecified ICE categories defined in the study SAP for those cases of study treatment discontinuation where reasons are not precisely captured by the eCRF. These cases will be identified by the GRADUATE Study Team after completion of data cleaning efforts

including medical data review. The predefined ICE categories are the following (specific ICEs may be added to the list if deemed necessary by the ACI):

Table 2 ICE Categories

Intercurrent Event (ICE)	SDCR/NSDCR
Withdrawal from study treatment due to lack of efficacy	SDCR
Withdrawal from study treatment due to safety or tolerability reason (NOTE: This will include discontinuations due to AE, incl. suspected or confirmed COVID-19 AEs)	SDCR
Withdrawal from study treatment with no informative reason given	SDCR
Withdrawal from study treatment due to the COVID-19 pandemic	NSDCR
Significant reduction in drug exposure due to the COVID-19 pandemic (defined as ≥ 4 missed dose-months)	NSDCR
Withdrawal from study treatment due to purely administrative reason	NSDCR
Death	NSDCR
Withdrawal from study treatment due to use or initiation of protocol prohibited medication	SDCR
Withdrawal from study treatment due to other SDCR ICEs	SDCR

The ACI will review discontinuation cases where the reason for study treatment discontinuation and substudy discontinuation is non informative and captured in the eCRF as 'Protocol deviation', 'Withdrawal by subject', 'Physician decision' or 'Other'. For these cases, free text is captured in the eCRF.

The ACI will review data provided by the GRADUATE Study Team (described in section 4.2). By carefully reviewing data relative to the ICEs, the ACI will help the GRADUATE Study Team achieve an objective classification of ICEs as SDCR or NSDCR.

4. COMMITTEE MEMBERSHIP

4.1 MEMBERS

The ACI is composed of a chair and two additional members. The Chair has the responsibility to digitally sign the ICEs Categorization Report and the form documenting that a meeting of the ACI took place.

Members: [redacted], MD
[redacted], [redacted]
F. Hoffmann-La Roche Ltd
([redacted])

[redacted]
F. Hoffmann-La Roche Ltd

[redacted]
F. Hoffmann-La Roche Ltd

4.2 ACI MEMBERS SELECTION CRITERIA

The ACI members may be employees of the Sponsor or any contract research organization that works with the Sponsor. The committee should include three members representing at least one of the following line functions: Clinical Science, Data Science, and Safety Science. ACI members should not have been involved in the conduct of Studies WN29922, WN39658, and related substudies, should not have been exposed to unblinding data of the studies in scope, and should have a minimum of two-years experience in clinical trials conduct. Based on the aforementioned criteria, ACI members will be selected by the GRADUATE Study Team.

Members of the ACI who do not fulfill all the selection criteria and whose ACI membership may materially affect objectivity will be asked to resign from the committee and will be replaced.

4.3 DURATION OF THE ACI MEMBERSHIP

The membership will extend for the duration of the Studies in scope (see Section 1), at least up to the time the database for primary analysis is locked and the study is unblinded to the Sponsor. If a member leaves the ACI, the GRADUATE Study Team will select a replacement based on the criteria described in section 3.2.

5. COMMITTEE MEETINGS

5.1 ORGANIZATIONAL MEETING

A first introduction meeting will formally establish the ACI and acquaint the ACI with the process that will be followed. In advance of the organizational meeting the committee will have received the study protocols, the IBs, the blank eCRF and the SAP (the latest draft if not yet final).

5.2 SCHEDULED MEETINGS

The number of meetings will depend on the amount of data to be reviewed by the ACI. The Study Team and the ACI will agree on the number of meetings to be held during the organizational meeting.

The Study Team will prepare reports including data to be reviewed. These reports will be provided to the ACI at least three business days prior to each meeting (Appendix 1). The content of these reports is limited to eCRF data extracted from:

- "Study Drug Completion/Early Discontinuation" form including :
  - "Completion/discontinuation reason" item
  - Free text field " If primary reason is protocol deviation, withdrawal by subject, physician decision or other, specify"

The data will be extracted from the eCRF and provided in a tabular format to the committee. ACI meetings will not be attended by the GRADUATE Study Team.
For ACI meetings to take place all three members should be attending. The decisions should be made in a unanimous way. However if this is not possible in some cases, the Chair has the casting vote.

6. COMMUNICATION AND DATA FLOW

6.1 COMMUNICATION

The GRADUATE study team will communicate to the ACI the meeting dates and the SPA responsible will extract data to be reviewed. The ACI will communicate the adjudicated ICEs to the GRADUATE Study Team and the SPA responsible (see section 5.2).

ACI members are to treat all communications regarding these clinical studies, including reports, data, review meeting discussions, teleconferences, and meeting minutes, as confidential material.

All communications relative to these meetings will be archived in the eTMF.

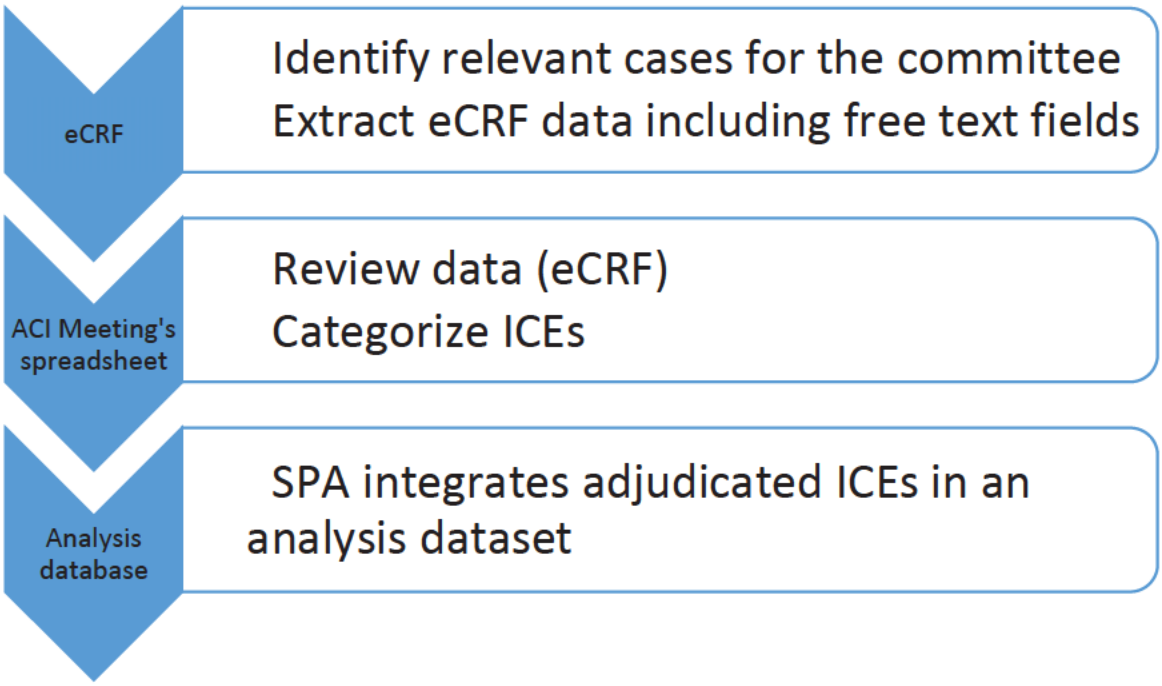
6.2 ICEs CATEGORIZATION REPORT

After each scheduled meeting, ACI will provide input on ICEs categorization during the meetings to the GRADUATE Study Team within seven business days. The format of ICEs Categorization Report will be in a tabular format. An example is presented in Appendix 2.

The GRADUATE Study Team will collect the outcome of ACI meetings, integrate them in an analysis dataset, and archive the documents in the eTMF.

7. APPENDIX 1

Organization flowchart



8. APPENDIX 2

The format of ICEs Categorization Report

Treatment discontinuation reason	Reason specification	ICE Categorization
Protocol deviation / Withdrawal by subject / Physician decision / Other	<eCRF free text>	Withdrawal from study treatment due to lack of efficacy / Withdrawal from study treatment due to safety or tolerability reason / etc.
etc.		

Signature Page for Final SAP WN29922/WN39658 (Graduate) v2 - Published
System identifier: RIM-CLIN-447214

Approval Task	[redacted] Company Signatory 29-Jul-2022 20:48:47 GMT+0000

PROTOCOL

TITLE:	**AN OPEN-LABEL, MULTICENTER, ROLLOVER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF LONG-TERM GANTENERUMAB ADMINISTRATION IN PARTICIPANTS WITH ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN42171
VERSION NUMBER:	1
EUDRACT NUMBER:	2020-000766-42
IND NUMBER:	102,266
NCT NUMBER:	To be determined
TEST PRODUCT:	Gantenerumab (RO4909832)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
07-Mar-2020 04:25:42	Company Signatory	[redacted]

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PROTOCOL ACCEPTANCE FORM

TITLE:	**AN OPEN-LABEL, MULTICENTER, ROLLOVER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF LONG-TERM GANTENERUMAB ADMINISTRATION IN PATIENTS WITH ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN42171
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IND NUMBER:	102,266
NCT NUMBER:	To be determined
TEST PRODUCT:	Gantenerumab (RO4909832)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form to your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**AN OPEN-LABEL, MULTICENTER, ROLLOVER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF LONG-TERM GANTENERUMAB ADMINISTRATION IN PARTICIPANTS WITH ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN42171
VERSION NUMBER:	1
EUDRACT NUMBER:	2020-000766-42
IND NUMBER:	102,266
NCT NUMBER:	To be determined
TEST PRODUCT:	Gantenerumab (RO4909832)
PHASE:	Phase IIIb
INDICATION:	Alzheimer's disease
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the safety, tolerability, and efficacy of long-term administration of open-label gantenerumab in participants with AD who completed Study WN29922 or WN39658. Specific objectives and corresponding endpoints for the study are outlined below.

Study Design

Description of Study

This is an open-label, multicenter, rollover study to evaluate the safety, tolerability, and efficacy of long-term administration of open-label gantenerumab in participants with AD who completed Study WN29922 or WN39658, either the double-blind or OLE part, as applicable (parent study). The blind to the study treatment allocation during the parent study will be maintained to protect study integrity.

Participants who have completed Study WN29922 or WN39658, either the double-blind or OLE part as applicable, will be eligible to participate in this study. Participants who discontinued early from study treatment during Study WN29922 or WN39658, regardless of the reason, will not be eligible for this study.

Informed consent should be obtained from participants while they are in the parent study. In special situations, informed consent can be obtained at a later timepoint upon discussion with Medical Monitor, and it must be obtained before any study procedures in this study are performed.

The first administration of gantenerumab in this study will be as follows:

- For participants who completed the double-blind part and did not enter the OLE part of Study WN29922 or WN39658: The first administration of open-label gantenerumab should take place approximately 2 weeks after the Week 104 visit of Study WN29922 or WN39658 and will be considered the OLE baseline visit (OLE Day 1).

- For participants who completed the double-blind part and the OLE part of Study WN29922 or WN39658, the first administration of gantenerumab in this study should take place approximately 2 weeks after the OLE Week 34 visit or the final dose visit in the Study WN29922 or WN39658 OLE. Participants who have a gap in their transition between the OLE part of the parent study (WN29922 or WN39658) and this study, for unforeseen reasons, will roll over to this study continuing the schedule of activities as per their last visit in the OLE part of the parent study (WN29922 or WN39658) upon discussion with the Medical Monitor.

Participants with evidence of ARIA-E on the last per-protocol study MRI scan report in Study WN29922 or WN39658, either its double-blind or OLE part, as applicable, will be retained in the WN29922 or WN39658 study until the ARIA-E finding is resolved. They may then enroll in Study WN42171. In these cases, the first visit of the participants in Study WN42171 will be adapted according to the schedule of the visits of each participant in the parent study.

The data from the last visit in the WN29922 or WN39658 studies (e.g., Week 104 or OLE Week 34, or last visit in the WN29922 or WN39658 OLE part) will be used as the data for the first visit in this study if the two visits take place within 4 weeks of each other. All cognitive scales, and the C-SSRS do not need to be repeated if they were performed within 6 months in the previous parent study. The MRI scan does not need to be repeated if performed within 6 months in the previous parent study (WN29922 or WN39658) and following the final study drug dose in the parent study. Vital signs and urine pregnancy test will have to be performed at the first visit in this study before dosing. MRI and urine pregnancy test results must be available before dosing.

In this study, participants who were in the active double-blind arm in the parent study will continue receiving open-label gantenerumab 510 mg SC Q2W, and those participants who were in the placebo double-blind arm will go through a full uptitration scheme while retaining the blinding to the previous treatment allocation. If there is a delay in a participant's transition between the OLE part of the parent study (WN29922 or WN39658) and this study (for instance, due to delays in the approval of this study at a site) that goes beyond a reasonable time frame as determined by the Sponsor, the participant may be asked to start at the dose they were at previously when they completed the parent study and to perform a safety MRI before receiving the target dose. In this case, such decisions will be made after discussion with the Medical Monitor.

The dosing schedule and the schedule of activities will be different for participants, depending on whether they completed the OLE part of the WN29922 or WN39658 studies, which covers the uptitration phase for the participants in the placebo arm, or if they completed only the double-blind part.

Following first visit assessments (i.e., OLE Day 1 either in this protocol or in the parent protocol), each participant will be treated for 2 years. The final dose of study drug will be administered at OLE Week 102. At the end of the treatment period, all participants will undergo an OLE Week 104 visit. Participants will be asked to come back for a follow-up visit at OLE Week 116.

Participants who discontinue study drug at any time during this study will be asked to complete an early termination visit 2 weeks after their final dose and also return for collection of safety data (except MRI) and limited efficacy data (i.e., secondary endpoints).

Participants who do not meet the criteria for participation in this study (screening failure) may be re-screened. The investigator will record reasons for screening failure in the screening log.

Substudies

The substudies associated with Study WN42171 will be described in separate protocols, and participants consenting to enroll in these substudies will be asked to sign the associated Informed Consent Forms. To date, two optional substudies are associated with Study WN42171: a longitudinal amyloid PET substudy and a longitudinal tau PET substudy.

The amyloid and tau PET assessments will enable a longitudinal evaluation of the effect of gantenerumab on brain amyloid deposition as measured by florbetaben or flutemetamol PET radioligands and tau burden as measured by [18F]GTP1 (an investigational radioligand for in vivo imaging of tau protein aggregates) in participants with AD.

The collected PET data are expected to help in understanding the effects of gantenerumab on amyloid and tau pathology over time as well as the relationship between changes in florbetaben/flutemetamol/[18F]GTP1-PET and changes in other endpoints in Study WN42171.

Two optional substudies associated with this protocol may be introduced.

In one of them, post-mortem brain tissue may be obtained from participants for evaluation of the effect of long-term gantenerumab therapy on the brain. The opportunity to donate post-mortem brain tissue may be discussed with participants.

In the other one, digital tools that assess the disease progression of the participants may be tested for validation and for other exploratory purposes.

Interested participants would be provided with additional details. Any further procedures, with respect to the optional substudies, will be governed by a separate consent form and separate substudy protocol document.

Independent Data Monitoring Committee

The iDMC will evaluate participant safety on a regular basis. In addition to the data defined in the iDMC Charter (e.g., the incidence and nature of adverse events, serious adverse events, adverse events of special interest, ARIA-E, ARIA-H, and ISRs), the iDMC will review all necessary cumulative data, including efficacy data if necessary, at regular intervals during the study. It is anticipated that these assessments will occur approximately every 3 months. At the time of each review, the iDMC will make appropriate recommendations (e.g., the study should continue as planned, the safety risk management should be modified, the protocol should otherwise be amended, and enrollment should be held pending further safety evaluations).

Decisions will be made after considering the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details, such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities are detailed in the iDMC Charter.

Final decisions will rest with the Sponsor.

Number of Patients

The planned enrollment is expected to be no more than approximately 2032 participants but will be determined by the number of participants who complete the WN29922 and WN39658 studies and enroll in this study.

Target Population

Inclusion Criteria

Participants must meet the following criteria for study entry:

- Signed Informed Consent Form by the participant with AD and/or the legal authorized representative as per local requirements
- Completed Study WN29922 or WN39658, either its double-blind part (participants have reached the 510 mg Q2W dose schedule by the time of completion) or OLE part (participants have received at least 3 doses of 510 mg Q4W), and did not discontinue study drug early
- Ability to comply with the study protocol
- Willingness and ability to complete all aspects of the study (including MRI and lumbar puncture [if applicable]).
- The participant should be capable of completing assessments either alone or with the help of the caregiver.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for at least 16 weeks after the final dose of gantenerumab.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to

surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Exclusion Criteria

Participants who meet any of the following criteria will be excluded from study entry:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within at least 16 weeks after the final dose of study drug

  Women of childbearing potential must have a negative urine pregnancy test at the final visit of the parent study.
- Prematurely discontinued from Study WN29922 or WN39658, either its double-blind or OLE part, as applicable, or from study drug, for any reason
- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Received any investigational treatment other than gantenerumab during or since completion of Study WN29922 or WN39658, either its double-blind or OLE part, as applicable
- Evidence of disseminated leptomeningeal hemosiderosis (i.e., more than three focal leptomeningeal hemosiderosis)
- Evidence of intracerebral macrohemorrhage
- Use of prohibited medication
- Evidence of ARIA-E on the last MRI scan report in Study WN29922 or WN39658, either its double-blind or OLE part, as applicable

  Participants should remain in the parent study, as governed by that protocol, and may enroll in this study once the ARIA-E is resolved.

End of Study

The end of this study is defined as the date when the last participant, last visit, occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last participant, whichever occurs later. The end of the study is expected to occur by the end of 2024.

In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of this study from baseline visit (OLE Day 1 in either the WN42171 protocol or in the parent protocol) to the end of the study (including the follow-up visit) is expected to be approximately 2 years and 3 months. Following uptitration, participants will receive up to 34 doses of gantenerumab 510 mg Q2W. Participants who did not participate in the OLE part of the parent study (WN29922 or WN39658) will also go through an uptitration scheme in the WN42171 study with a duration of at least 34 weeks.

Investigational Medicinal Products

The investigational medicinal product (IMP) for this study is gantenerumab.

Test Product (Investigational Drug)
Gantenerumab or placebo will be administered by SC injection to all patients.

Statistical Methods

Primary Analysis
The safety analysis population will include all enrolled participants who received at least one dose of study drug in this protocol.

The following safety outcome measures will be summarized using descriptive statistics:

- Nature, frequency, severity, timing, and outcomes of adverse events and serious adverse events
- Physical examinations (including neurological systems), vital signs, blood tests, and C-SSRS
- Nature, frequency, severity, and timing of ARIA-E and ARIA-H
- Nature, frequency, severity, timing, and outcomes of injection-site reactions
- Incidence of treatment discontinuations for adverse events
- Incidence of adverse events of special interest

Statistical methods, endpoint definitions, and analyses of the safety endpoints will be described in the SAP.

Determination of Sample Size

The sample size will include all eligible participants who consent to this study. The sample size is expected to be no more than approximately 2032 participants but will be determined by the number of participants who complete the WN29922 and WN39658 studies and enroll in this study.

Interim Analyses
To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one or more interim efficacy analysis(es). An interim analysis may be considered when the parent pivotal studies WN29922 and WN39658 are completed and the submission folder is under preparation. Details will be pre-specified in the SAP.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Aβ	amyloid beta
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADA	anti-drug antibody
ADAS-Cog11	Alzheimer's Disease Assessment Scale–Cognition, Subscale 11
ADAS-Cog13	Alzheimer's Disease Assessment Scale–Cognition, Subscale 13
ADCS-ADL	Alzheimer's Disease Cooperative Study Group–Activities of Daily Living
ADL	activities of daily living
ARIA	amyloid-related imaging abnormality
ARIA-E	amyloid-related imaging abnormality–edema/effusion
ARIA-H	amyloid-related imaging abnormality–microhemorrhage/hemosiderin deposition
BOLD	blood oxygenation level-dependent
CDR	Clinical Dementia Rating
CDR-GS	Clinical Dementia Rating–Global Score
CDR-SOB	Clinical Dementia Rating–Sum of Boxes
COA	clinical outcome assessment
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CTAD	Clinical Trials in Alzheimer's Disease
DTI	diffuse tensor imaging
EC	Ethics Committee
eCRF	electronic Case Report Form
EQ-5D	EuroQol 5-Dimension Questionnaire
EQ-5D-5L	EuroQoL-5-Dimension, 5-Level Questionnaire
FA	fractional anisotropy
FAQ	Functional Activities Questionnaire
FDA	(U.S.) Food and Drug Administration
GRE	gradient recalled echo
HbA_{1C}	hemoglobin A_{1c}
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product

IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ISR	injection-site reaction
IxRS	interactive voice or web-based response system
MAD	multiple ascending dose
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
MN	Mobile Nursing
NMDA	N-methyl-D-aspartate
NPI-Q	Neuropsychiatric Inventory Questionnaire
OLE	open-label extension
PD	pharmacodynamic
PET	positron emission tomography
PK	pharmacokinetic
p-tau	phosphorylated tau
QoL-AD	Quality of Life–Alzheimer's Disease scale
Q2W	every 2 weeks
Q4W	every 4 weeks
QoL	quality of life
QoL-AD	Quality of Life–Alzheimer's Disease
RBR	Research Biosample Repository
rs-fMRI	resting-state functional magnetic resonance imaging
RUD-Lite	Resource Utilization in Dementia–Lite
SAP	Statistical Analysis Plan
t-tau	total tau
thyroxine	T4
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing
ZCI-AD	Zarit Caregiver Interview for Alzheimer’s Disease

1. BACKGROUND

1.1 BACKGROUND ON ALZHEIMER'S DISEASE

The World Health Organization estimates that around 50 million people worldwide are diagnosed with dementia and that there are 10 million new cases every year. The total number of people with dementia is estimated to reach 82 million in 2030 and will more than triple to 152 million by 2050. Alzheimer's disease (AD) is the most common form of dementia, accounting for 60%–70% of cases (World Health Organization 2019). The prevalence of AD increases with age, with a global prevalence of 5%–8% in people 60 years and older. Because of its increasing prevalence, long duration, and high cost of care, AD is expected to continue to represent a major public health problem for decades to come.

The median survival time following a diagnosis of AD strongly depends on the patient's age at diagnosis and ranges from 8.3 years for persons diagnosed with AD at 65 years old to 3.4 years for those 90 years old (Brookmeyer et al. 2002; Zanetti et al 2009), but some individuals survive as long as 20 years.

It is well recognized that in comparison to other therapeutic domains, there is a real unmet medical need in AD therapy (Gauthier et al. 2016). To date, only five medications have received marketing approval in the European Union and United States to treat the symptoms of AD, including acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists. These approved drugs are recognized to temporarily improve some clinical symptoms of AD in some patients but do not modify progression of the disease (Cummings et al. 2018).

Currently, one compelling therapeutic target (Graham et al. 2017) is amyloid beta (Aβ), and Aβ-targeting therapies remain the major trend in AD drug development (Bachurin et al. 2017). These therapies are based on the amyloid hypothesis that posits Aβ accumulation as the primary factor driving AD pathogenesis (Selkoe 1991; Hardy and Selkoe 2002; Selkoe and Hardy 2016). This Aβ accumulation in the brain begins well before the development of clinical dementia in AD and causes a series of downstream events leading to synaptic dysfunction, inflammation, neurodegeneration, and clinical symptoms. For these reasons, treatments that prevent, slow, or decrease the accumulation of brain Aβ are being tested as therapeutic agents in AD.

1.2 BACKGROUND ON GANTENERUMAB

Gantenerumab (or RO4909832) is a recombinant, human monoclonal antibody of the IgG1 subclass directed against the Aβ peptide. Gantenerumab recognizes a conformational epitope of Aβ and has demonstrated activity for both major types of Aβ (Aβ1-40, Aβ1-42). In vitro, gantenerumab recognizes synthetic aggregated Aβ fibrils and Aβ oligomers with high nanomolar affinity (K_D, ~0.6–1.2 nM). The mechanism of action of gantenerumab is primarily clearance of Aβ plaques by antibody-dependent

cell-mediated phagocytosis. Gantenerumab also works via dissociation of Aβ peptide aggregates by direct resolution and by blockade of toxic Aβ oligomers.

Gantenerumab is manufactured by cell culture of a recombinant Chinese hamster ovary K1 mammalian cell line and subsequent purification of the antibody. Gantenerumab drug substance manufacturing was optimized during development to improve process robustness and increase overall process yield, leading to several generations of manufacturing process (G1, G2, G3, and G4). Drug material manufactured by the G4 process is used in pivotal Phase III clinical trials (Studies WN29922 and WN39658). G4 drug material will be used in this study.

1.2.1 Nonclinical and Clinical Studies

Preclinical evidence has suggested that monoclonal Aβ antibodies may be able to remove and reduce deposition of Aβ aggregates from the brain. In transgenic animal models of AD, vaccination with Aβ or passive immunization with anti-Aβ antibodies resulted in decreased amyloidosis and in improvement of memory function in some transgenic models of cognitive function (Janus et al. 2000). Accumulating clinical evidence also supports that monoclonal Aβ antibodies can bind Aβ and promote its clearance (Salloway et al. 2009; Ostrowitzki et al. 2012; Klein et al. 2019b), reduce deposition of Aβ aggregates, and reduce markers of neurodegeneration in the cerebrospinal fluid (CSF) (Roche Research Report No. 1066251). In a Phase I study with the anti-Aβ monoclonal antibody aducanumab, reduction of deposited amyloid as shown on brain amyloid positron emission tomography (PET) imaging was associated with a time- and dose-related slowing of cognitive decline (Sevigny et al. 2016). Because the pathological changes associated with AD develop decades before clinical symptoms emerge, it is thought that earlier intervention may be more effective in arresting or delaying disease progression (Sevigny et al. 2016). Consequently, therapies targeting this process have the potential to significantly alter the progression of the disease. Gantenerumab, a fully human monoclonal antibody targeting aggregated forms of Aβ, such as Aβ oligomers, fibrils, and plaques, is expected to address this need (Bohrmann et al. 2012).

Gantenerumab has been investigated in 10 completed Phase I clinical studies: 3 single ascending dose studies in healthy volunteers and patients with mild to moderate AD (BN18726, JP22474, and BP30042); 2 multiple ascending dose (MAD) studies of patients with mild to moderate AD (NN19866 and JP22431); and 4 bioavailability studies in healthy subjects–one comparing the IV and SC formulations of gantenerumab (WP22461), two comparing lyophilized and high-concentration liquid formulations of gantenerumab (WP27951 and BP29113), and one comparing drug substance manufactured through the third and fourth generation (G3 and G4) processes (WP40052). A tolerability study that compared injection-site pain between faster and slower SC administration of gantenerumab was also conducted (WP39322). Overall, a total of 543 subjects have participated in the Phase I studies; of these participants,

406 healthy volunteers and 101 patients with mild to moderate AD have received gantenerumab.

Based on results of the MAD Study (NN19866) and of the relative bioavailability study (WP27951), the doses of 105 mg SC every 4 weeks (Q4W) (equivalent to 60 mg IV Q4W) and 225 mg SC Q4W (equivalent to 130 mg IV Q4W) were initially selected for the Phase III studies WN25203 and WN28745. Following the results of the WN25203 futility analysis, these studies were converted into open-label extensions (OLEs) to examine the safety and tolerability of a higher dose of gantenerumab (1200 mg SC Q4W).

Overall, 383 patients enrolled in the OLEs of studies WN25203 and WN28745. As of 1 May 2019, 363 patients had been exposed to G3 gantenerumab doses higher than 225 mg, and 309 patients reached the target 1200 mg dose. Continuous monitoring of safety data and magnetic resonance imaging (MRI) findings by the Sponsor has not identified any new safety signals in these ongoing studies. Injection-site reactions (ISRs) and amyloid-related imaging abnormalities (ARIAs) remain the only identified risks for gantenerumab. These OLE studies end in 2020, and patients who have not discontinued study treatment at the end of the prescribed study period will be provided an option to enroll in an open-label rollover study to evaluate the safety and tolerability of long-term administration of gantenerumab (WN41874).

Based on safety results from OLE studies WN25203 and WN28745, and on data from the PET substudies that confirmed the pharmacodynamic (PD) effects of gantenerumab treatment (1200 mg SC Q4W) on Aβ plaque reduction (Klein et al. 2019b), two pivotal multicenter, Phase III studies in patients with early (prodromal to mild) AD were initiated: WN29922 (Graduate 1) and WN39658 (Graduate 2). These studies are examining the efficacy, safety, and tolerability of gantenerumab uptitrated to 510 mg Q2W dosing; they are currently ongoing and are expected to be completed in 2023. Refer to the Gantenerumab Investigator's Brochure for more details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.3.1 Study Rationale

Study WN42171 allows participants previously treated with gantenerumab or placebo for approximately 2 years in the parent Studies WN22992 or WN39658 to continue receiving open-label gantenerumab.

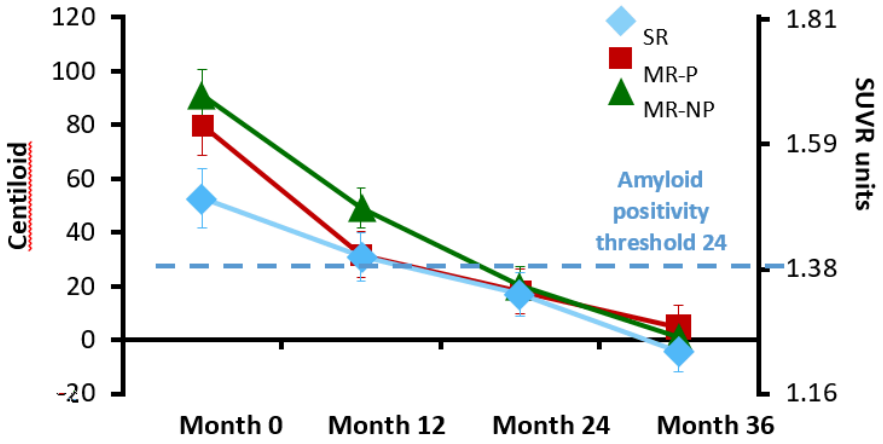
Currently, approved therapies for AD focus on symptomatic approaches that target synaptic function and cognitive enhancement (Cummings 2004). However, the amyloid hypothesis suggests that overproduction of Aβ or failure to effectively clear this peptide contributes to AD (Selkoe and Hardy 2016) and that accumulation of Aβ peptides is a factor contributing to AD progression (Sun et al. 2015). Thus, the targeting of Aβ and subsequent displacement of Aβ from the brain is a rational approach to modify AD progression.

Accumulating clinical evidence supports that monoclonal Aβ antibodies can bind Aβ and promote its clearance (Salloway et al. 2009; Ostrowitzki et al. 2012; Sevigny et al. 2016; Klein et al. 2019b), reduce deposition of Aβ aggregates, and reduce markers of neurodegeneration in CSF (Ostrowitzki et al. 2017). A Phase I study of aducanumab (Sevigny et al. 2016) and a Phase II study of BAN2401 (Swanson et al. 2018) suggested that reduction of deposited amyloid, as seen on brain amyloid PET imaging, was associated with a dose-related slowing of cognitive decline.

Gantenerumab data from the PET substudies of the WN25203 and WN28745 OLEs confirmed that gantenerumab treatment at a dose of 1200 mg SC Q4W reduced Aβ plaques in patients with AD (Klein et al. 2019b). Overall, 89 patients from the OLEs of the WN25203 and WN28745 studies were included in amyloid PET substudies using florbetapir F18. As of 31 August 2019, of these 89 patients, 67 patients received follow-up scans at Week 52, 42 patients at Week 104, and 30 patients at Week 156 of the OLE.

Results of the PET substudies showed a marked and consistent reduction of amyloid load in patients receiving higher-dose gantenerumab in all three patient groups that were analyzed (Figure 1): 1) MR-DBP (patients in the placebo arm of Study WN28745); 2) MR-DBA (patients in the active treatment arm of Study WN28745); and 3) SR (patients from Study WN25203). Indeed, amyloid reductions were seen consistently in nearly all patients in the three analyzed subgroups (Figure 2).

Figure 1 Mean (SE) PET Amyloid Reductions in the OLE PET Substudies



Centiloids[a]

SR	52.7 (11.1) n = 20	30.9 (8.9) n = 19	17.0 (8.2) n = 13	**–4.3 (7.5)** n = 10
MR-P	79.6 (10.9) n = 21	31.7 (8.6) n = 21	18.1 (8.3) n = 11	**4.7 (8.0)** n = 8
MR-NP	91.1 (9.6) n = 27	49.1 (7.6) n = 27	20.2 (7.0) n = 18	**0.78 (6.7)** n = 12

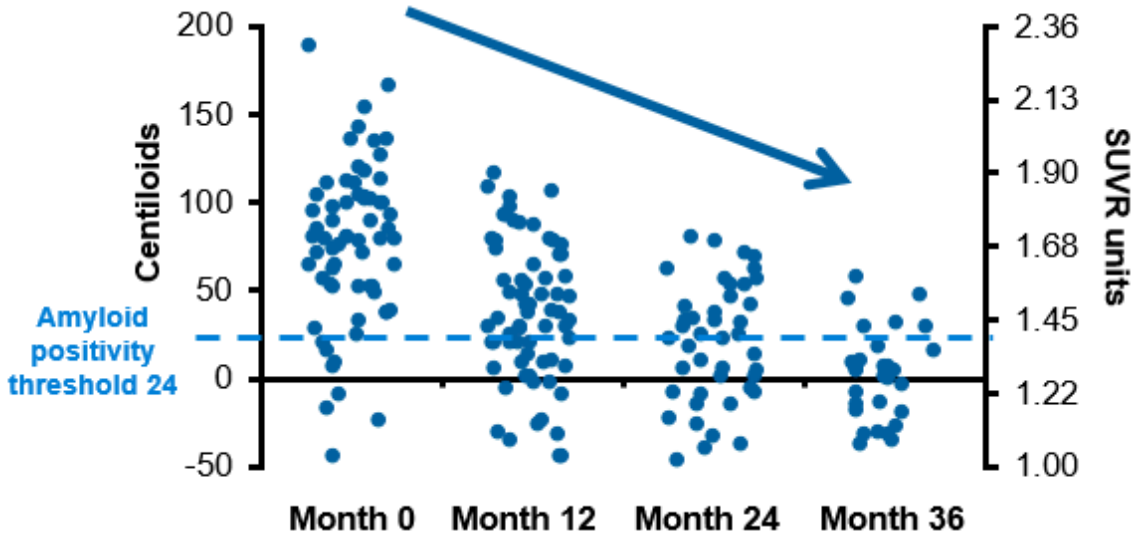
MR-DBA = Marguerite RoAD (WN28745) double-blind active (patients in the active treatment arm of Study WN28745 during the double-blind phase); MR-DBP = Marguerite RoAD (WN28745) double-blind placebo (patients in the placebo arm of Study WN28745 during the double-blind phase); OLE = open-label extension; PET = positron emission tomography; SE = standard error; SR = Scarlet RoAD (WN25203); SUVR = standardized uptake value ratio.

[a] Analyzed using a mixed-model for repeated measures.

Source: Klein et al. 2019a.

The threshold for amyloid positivity is an important anchor for interpreting the PET substudy results. It is defined as the quantitative threshold that best discriminates pathologically-verified absence of plaques or sparse plaques from moderate to frequent plaques. A centiloid value of 24 is generally recognized as the amyloid positivity threshold (Landau and Jagust 2015; Navitsky et al. 2018; Klein et al. 2019b). Results in the ongoing substudies of WN25203 and WN28745 confirm the amyloid plaque removal component of the gantenerumab mechanism of action. The results further show that following 3 years of gantenerumab treatment, 80% of subjects were below the positivity threshold, and 43% of subjects were below a centiloid value of 0, which represents the mean amyloid load of a healthy normal population (Figure 2).

Figure 2 Patient-Level Amyloid Reductions over 3 Years of Treatment in the OLE PET Substudies



Proportion of participants below amyloid positivity threshold

No. of participants	68	67	42	30
% below threshold	**15%**	**37%**	**52%**	**80%**

OLE = open-label extension; PET = positron emission tomography; SUVR = standardized uptake value ratio.
Source: Klein et al. 2019a.

In summary, the PET substudy results demonstrate continued amyloid removal beyond 2 years of gantenerumab treatment. Thus, this study, which provides open-label gantenerumab for 2 additional years to patients already receiving gantenerumab in the parent study (WN22992 or WN39658), will provide valuable information on how continued amyloid removal may translate into continued clinical effect.

Study WN42171 will also provide the opportunity for participants previously treated with placebo in the double-blind phase of Study WN22992 or WN39658 to receive gantenerumab treatment for up to 2 years. To protect study data integrity and to aid the assessment of the long-term effects of gantenerumab, treatment assignment information from the double-blind phase of Study WN22992 or WN39658 will remain blinded to the Sponsor, investigator, and participant at least until database lock of the parent studies, which will happen while this study is ongoing.

1.3.2 Safety Overview

Nonclinical characterization of gantenerumab did not show relevant safety findings. No differences between gantenerumab and placebo groups have been observed in laboratory parameters, physical and neurologic examinations, vital signs, or ECG parameters.

The identified risks of gantenerumab treatment are ARIAs and ISRs. Safety data and MRI findings are continuously monitored in all ongoing studies, and no new safety signals have been identified.

The Gantenerumab Investigator's Brochure includes a summary of safety data with gantenerumab SC in participants with AD from Studies WN25203 and WN28745 as well as from Phase I studies with gantenerumab SC and IV.

Providing participants who complete study treatment in the pivotal Studies WN22992 and WN39658 with an opportunity to extend or initiate treatment with open-label gantenerumab in Study WN42171 will allow the collection of more information on the long-term safety and tolerability of gantenerumab in AD. It will also provide more information on its efficacy in the context of long-term exposure. Furthermore, the OLE will increase the overall number of participants exposed to gantenerumab and participant-years of exposure, thus increasing understanding of the safety and efficacy profiles.

1.3.2.1 Amyloid-Related Imaging Abnormalities

ARIAs are one of the most significant adverse events reported in therapies against aggregated forms of Aβ. These findings appear to be dependent on dose-, time-, and apolipoprotein E gene allele ε4- (*APOE* ε4-) (Piazza and Winblad 2016).

The mechanism underlying the development of amyloid-related imaging abnormality–edema/effusion (ARIA-E) and amyloid-related imaging abnormality-microhemorrhage/hemosiderin deposition (ARIA-H) during anti-amyloid treatment is not yet fully understood. Because antibodies remove Aβ from both the parenchyma and cerebral vasculature, vessels with preexisting amyloid vascular pathology might become transiently more susceptible to leakage of vascular contents. This pathology results in ARIA-E if the leakage consists of proteinaceous fluid and in ARIA-H if the leakage consists of blood products (Sperling et al. 2012). An anti-Aβ therapy that effectively maintains vascular Aβ clearance would allow vascular remodeling and might, over time, decrease the risk of such extravasation events (Sperling et al. 2012). This is consistent with experiences in previous and ongoing studies and with reported data from the long-term extension study of aducanumab treatment (Viglietta et al. 2016).

Understanding of the clinical significance of ARIA by study sponsors, investigators, and regulators has substantially evolved since ARIA events were first seen on MRI scans in a Phase I clinical trial with bapineuzumab (Black et al. 2010). The accrued clinical

evidence with gantenerumab and other N-terminus anti-amyloid antibodies has shown that ARIA events tend to occur early in treatment, are dose- and *APOE* ε4-dependent, and can be monitored by MRI and managed with dose intervention algorithms.

The Sponsor's experience with managing patients with ARIA findings and increasing understanding of the impact of such findings on patient clinical outcomes has resulted in the introduction of revised ARIA risk mitigation measures in studies with gantenerumab over time. Accordingly, ARIA management has shifted from more cautious management, where an ARIA-E finding resulted in treatment interruption regardless of intensity (Study WN25203 [double-blind]), to less restrictive management, where only moderate-severe intensity ARIA-E and symptomatic ARIA-E findings result in treatment interruption (Studies WN25203 and WN28745: OLE; Studies WN29922 and WN39658). Similarly, the cumulative number of ARIA-H findings that trigger treatment discontinuation was changed from 5 (Studies WN25203 and WN28745 [double-blind]) to 10 (Studies WN25203 and WN28745 [OLE]), to 15 (Studies WN29922 and WN39658). The revised management led to similar and acceptable safety profiles. In WN29922 and WN39658 studies, safety reviews of unblinded data by an independent Data Monitoring Committee (iDMC) have not identified any new safety signal.

Taking into account the evolving experience with managing ARIA findings, including the finding that continued gantenerumab treatment during episodes of asymptomatic mild ARIA-E was not associated with clinically unfavorable outcomes, the Sponsor intends to examine the safety of continuing gantenerumab treatment through mild to moderate asymptomatic ARIA-E findings and to examine the safety of gantenerumab therapy in the presence of an increased number of ARIA-H microhemorrhages.

Study WN42171 will require an MRI scan documenting the absence of ARIA-E or evidence of disseminated leptomeningeal hemosiderosis prior to the first gantenerumab dose. If ARIA findings occur during the study, MRI monitoring, temporary dose holding, or permanent study drug discontinuation will be implemented according to an ARIA management plan, as described in Appendix 2.

Safety findings, including individual participant and aggregate data, will be reviewed on a regular basis by the Sponsor and by an iDMC.

1.3.2.2 Injection-Site Reactions

The incidence of ISRs in gantenerumab-treated patients with up to the target gantenerumab dose (1200 mg SC Q4W) ranged from 36% (Study WN25203) to 38% (Study WN28745 OLE) as of 1 May 2019. All ISRs were non-serious, mostly mild to moderate in intensity, and the majority resolved without treatment. The most common signs and symptoms of ISRs included injection-site erythema, redness, swelling, and itching. No patients discontinued study treatment due to ISRs.

1.3.2.3 Overall Benefit–Risk Summary

The benefit-risk assessment of gantenerumab treatment in Study WN42171 is based on the following:

- Gantenerumab has shown evidence of continuous reduction of the amyloid plaque component in up to 3 years of treatment and thus shows potential benefit in slowing the progression of AD.
- Findings from Study WN25203 (Klein et al. 2019), the PRIME study with aducanumab (Sevigny et al. 2016), and from the Phase II study with BAN2401 (Swanson et al. 2018) suggest that reduction in deposited amyloid is associated with a dose-related slowing of cognitive decline, providing additional support for the hypothesis that anti-amyloid treatment may be associated with a beneficial clinical effect.
- Results from the double-blind part of Studies WN25203 and WN28745, as well as from the ongoing OLEs of Studies WN25203 and WN28745, showed that ARIA-E findings are mostly asymptomatic, non-serious, of mild severity, and do not require permanent cessation of treatment.
- No new safety signals have been identified from the ongoing Phase III studies with gantenerumab with doses of up to 510 mg Q2W or equivalent, which supports the safety of continued administration of gantenerumab uptitrated to the target dose in the current and planned studies, including Study WN42171.
- Study WN42171 will provide participants with the opportunity to extend treatment with gantenerumab beyond 2 years, thereby providing more information on the long-term safety, tolerability, and efficacy of gantenerumab in AD. Furthermore, the study will increase the overall number of participants exposed to gantenerumab and the patient-years of exposure and increase the understanding of the safety:efficacy profile. Analyzing the long-term safety, tolerability, and efficacy of gantenerumab is of critical importance to help clinicians make informed therapeutic decisions for participants.
- The design of Study WN42171 will allow participants with moderate asymptomatic ARIA-E and with any number of ARIA-H microhemorrhages to continue gantenerumab treatment. This is in line with the evolving understanding of the clinical significance of ARIA by the clinical trial Sponsors and medical community (see Section 3.3.4).
- An iDMC will evaluate safety data on a regular basis, including the incidence and nature of adverse events, serious adverse events, adverse events of special interest, ARIA-E, ARIA-H, and ISRs and will make appropriate recommendations (see Section 3.1.3).

Overall, the benefit–risk profile of gantenerumab supports open-label gantenerumab treatment in Study WN42171 for participants who completed either the double-blind or OLE part of Study WN29922 or WN39658.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, tolerability, and efficacy of long-term administration of open-label gantenerumab in participants with AD who completed Study WN29922 or WN39658. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 SAFETY OBJECTIVE

2.1.1 Primary Objective: Safety

The primary objective for this study is to evaluate the safety and tolerability of long-term gantenerumab administered by SC injection on the basis of the following endpoints:

- Nature, frequency, severity, and timing of adverse events and serious adverse events
- Physical examinations (including neurologic systems), vital signs, blood tests, and Columbia-Suicide Severity Rating Scale (C-SSRS)
- Nature, frequency, severity, and timing of ARIA-E and ARIA-H
- Nature, frequency, severity, and timing of ISRs

2.2 EFFICACY OBJECTIVE

2.2.1 Secondary Objective: Efficacy

The secondary objective for this study is to evaluate the efficacy of long-term gantenerumab administered by SC injection on the basis of the following endpoint:

- Change over time in cognition, function, and other outcomes as measured by the following:
  - Clinical Dementia Rating (CDR)
  - Mini-Mental State Examination (MMSE)
  - Alzheimer Disease Assessment Scale–Cognition, Subscale 11 (ADAS-Cog11) and Alzheimer Disease Assessment Scale–Cognition, Subscale 13 (ADAS-Cog13)
  - Verbal Fluency Task
  - Coding
  - Functional Activities Questionnaire (FAQ)
  - Alzheimer Disease Cooperative Study Group–Activities of Daily Living (ADCS-ADL)

2.2.2 Exploratory Objective: Efficacy

The exploratory objective for this study is to evaluate the efficacy of long-term gantenerumab administered by SC injection on the basis of the following endpoint:

- Change over time as measured by the following:
  - Health-related quality of life, as assessed by the Quality of Life–Alzheimer's Disease (QoL-AD) scale
  - Behavioral and neuropsychiatric symptoms of AD, as measured by the Neuropsychiatric Inventory Questionnaire (NPI-Q)
  - Caregiver burden, as assessed by the Zarit Caregiver Interview for Alzheimer's Disease (ZCI-AD) scale
  - Elements of resource utilization, as assessed by the Resource Utilization in Dementia–Lite (RUD-Lite)

2.3 PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objective for this study is to characterize the PK profile of gantenerumab administered by SC injection on the basis of the following endpoint:

- Plasma concentration of gantenerumab administered SC at specified timepoints

2.4 IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is to evaluate the immune response to gantenerumab administered by SC injection on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study

2.5 BIOMARKER OBJECTIVE

The biomarker objective for this study is to evaluate the long-term effects of gantenerumab administered by SC injection on the basis of the following endpoints:

- Brain amyloid load over time, as measured by amyloid PET scan in a subset of participants
- Brain tau load over time, as measured by tau PET scan in a subset of participants
- CSF markers of disease over time in a subset of participants, including, but not limited to, $A\beta_{1-42}$, total tau (t-tau), and phosphorylated tau (p-tau)
- MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures; changes in functional brain connectivity; or changes in the integrity of white matter in all participants
- Blood and Plasma markers over time

2.6 HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate the health status utility scores of participants treated with gantenerumab on the basis of the following endpoint:

- Health outcomes in participant and caregiver, as measured by EuroQol 5-Dimension Questionnaire (EQ-5D)

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is an open-label, multicenter, rollover study to evaluate the safety, tolerability, and efficacy of long-term administration of open-label gantenerumab in participants with AD who completed Study WN29922 or WN39658, either the double-blind or OLE part, as applicable (parent study). The blind to the study treatment allocation during the parent study will be maintained to protect study integrity.

Participants who have completed Study WN29922 or WN39658, either the double-blind or OLE part as applicable, will be eligible to participate in this study. Participants who discontinued early from study treatment during Study WN29922 or WN39658, regardless of the reason, will not be eligible for this study.

Informed consent should be obtained from participants while they are in the parent study. In special situations, informed consent can be obtained at a later timepoint upon discussion with Medical Monitor, and it must be obtained before any study procedures in this study are performed.

The first administration of gantenerumab in this study will be as follows:

- For participants who completed the double-blind part and did not enter the OLE part of Study WN29922 or WN39658: The first administration of open-label gantenerumab should take place approximately 2 weeks after the Week 104 visit of Study WN29922 or WN39658 and will be considered the OLE baseline visit (OLE Day 1).
- For participants who completed the double-blind part and the OLE part of Study WN29922 or WN39658, the first administration of gantenerumab in this study should take place approximately 2 weeks after the OLE Week 34 visit or the final dose visit in the Study WN29922 or WN39658 OLE. Participants who have a gap in their transition between the OLE part of the parent study (WN29922 or WN39658) and this study, for unforeseen reasons, will roll over to this study continuing the schedule of activities as per their last visit in the OLE part of the parent study (WN29922 or WN39658) upon discussion with the Medical Monitor.

Participants with evidence of ARIA-E on the last per-protocol study MRI scan report in Study WN29922 or WN39658, either its double-blind or OLE part, as applicable, will be

retained in the WN29922 or WN39658 study until the ARIA-E finding is resolved. They may then enroll in Study WN42171. In these cases, the first visit of the participants in Study WN42171 will be adapted according to the schedule of the visits of each participant in the parent study.

The data from the last visit in the WN29922 or WN39658 studies (e.g., Week 104 or last visit in the WN29922 or WN39658 OLE part) will be used as the data for the first visit in this study if the two visits take place within 4 weeks of each other. All cognitive scales, and the C-SSRS do not need to be repeated if they were performed within 6 months in the previous parent study. The MRI scan does not need to be repeated if performed within 6 months in the previous parent study (WN29922 or WN39658) and following the final study drug dose in the parent study. Vital signs and urine pregnancy test will have to be performed at the first visit in this study before dosing. MRI and urine pregnancy test results must be available before dosing.

In this study, participants who were in the active double-blind arm in the parent study will continue receiving open-label gantenerumab 510 mg SC Q2W, and those participants who were in the placebo double-blind arm will go through a full uptitration scheme while retaining the blinding to the previous treatment allocation. Details of the dosing scheme are described in Section 4.3.2. If there is a delay in a participant's transition between the OLE part of the parent study (WN29922 or WN39658) and this study (for instance, due to delays in the approval of this study at a site) that goes beyond a reasonable time frame as determined by the Sponsor, the participant may be asked to start at the dose they were at previously when they completed the parent study and to perform a safety MRI before receiving the target dose. In this case, such decisions will be made after discussion with the Medical Monitor.

The dosing schedule and the schedule of activities will be different for participants, depending on whether they completed the OLE part of the WN29922 or WN39658 studies, which covers the uptitration phase for the participants in the placebo arm, or if they completed only the double-blind part. Details are described in Appendix 1.

Following baseline assessments (i.e., OLE Day 1 either in this protocol or in the parent protocol), each participant will be treated for 2 years. The final dose of study drug will be administered at OLE Week 102. At the end of the treatment period, all participants will undergo an OLE Week 104 visit. Participants will be asked to come back for a follow-up visit at OLE Week 116.

Participants who discontinue study drug at any time during this study will be asked to complete an early termination visit 2 weeks after their final dose and also return for collection of safety data (except safety MRI) and limited efficacy data (i.e., secondary endpoints) (see Section 4.6.1).

Participants who do not meet the criteria for participation in this study (screening failure) may be re-screened. The investigator will record reasons for screening failure in the screening log (Section 4.5.1).

3.1.2 Substudies

The substudies associated with Study WN42171 will be described in separate protocols, and participants consenting to enroll in these substudies will be asked to sign the associated Informed Consent Forms. To date, two optional substudies are associated with Study WN42171: a longitudinal amyloid PET substudy and a longitudinal tau PET substudy.

The amyloid and tau PET assessments will enable a longitudinal evaluation of the effect of gantenerumab on brain amyloid deposition as measured by florbetaben or flutemetamol PET radioligands and tau burden as measured by [^{18}F]GTP1 (an investigational radioligand for in vivo imaging of tau protein aggregates) in participants with AD.

The collected PET data are expected to help in understanding the effects of gantenerumab on amyloid and tau pathology over time as well as the relationship between changes in florbetaben/flutemetamol/[^{18}F]GTP1-PET and changes in other endpoints in Study WN42171.

Two optional substudies associated with this protocol may be introduced.

In one of them, post-mortem brain tissue may be obtained from participants for evaluation of the effect of long-term gantenerumab therapy on the brain. The opportunity to donate post-mortem brain tissue may be discussed with participants.

In the other one, digital tools that assess the disease progression of the participants may be tested for validation and for other exploratory purposes.

Interested participants would be provided with additional details. Any further procedures, with respect to the optional substudies, will be governed by a separate consent form and separate substudy protocol document.

3.1.3 Independent Data Monitoring Committee

The iDMC will evaluate participant safety on a regular basis. In addition to the data defined in the iDMC Charter (e.g., the incidence and nature of adverse events, serious adverse events, adverse events of special interest, ARIA-E, ARIA-H, and ISRs), the iDMC will review all necessary cumulative data, including efficacy data if necessary, at regular intervals during the study. It is anticipated that these assessments will occur approximately every 3 months. At the time of each review, the iDMC will make appropriate recommendations (e.g., the study should continue as planned, the safety

risk management should be modified, the protocol should otherwise be amended, and enrollment should be held pending further safety evaluations).

Decisions will be made after considering the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details, such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities are detailed in the iDMC Charter.

Final decisions will rest with the Sponsor.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last participant, last visit, occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last participant, whichever occurs later. The end of the study is expected to occur by the end of 2024.

In addition, the Sponsor may decide to terminate the study at any time.

The total length of this study from baseline visit (OLE Day 1 in either the WN42171 protocol or in the parent protocol) to the end of the study (including the follow-up visit) is expected to be approximately 2 years and 3 months. Following uptitration, participants will receive up to 34 doses of gantenerumab 510 mg Q2W. Participants who did not participate in the OLE part of the parent study (WN29922 or WN39658) will also go through an uptitration scheme in the WN42171 study with a duration of at least 34 weeks.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Gantenerumab Dose and Titration Schedule

All participants will receive a target dose of 510 mg gantenerumab SC Q2W, which is the same as the target dose received in the parent study. Participants who will be receiving gantenerumab for the first time in the WN42171 study will follow a titration schedule with a low starting dose and gradual increase in dosing that is expected to reduce the risk of ARIA-E for both *APOE* carriers and non-carriers, which was also followed in the WN29922 and WN39658 studies.

3.3.2 Rationale for Participant Population

Participants with AD who completed Study WN29922 or WN39658, either the double-blind or OLE part, as applicable, will be eligible to participate in this study in order to evaluate the safety, tolerability, and efficacy of long-term gantenerumab administration. Additionally, participants in the placebo double-blind arm in the parent studies will get exposure to potentially active treatment.

3.3.3 Rationale for Study Treatment Duration

In order to collect safety, tolerability, and efficacy data for long-term gantenerumab administration, this study will provide open-label gantenerumab to participants who completed Study WN29922 or WN39658, either its double-blind or OLE part, as applicable, for 2 years starting from baseline (OLE Day 1 in either this protocol or the parent protocol). With the 2-year duration, participants in the placebo double-blind arm in the parent studies will receive the full 2 years of therapy, like their co-participants who were in the active double blind arm.

3.3.4 Rationale for ARIA Management Rules

In previous studies with gantenerumab, the Sponsor used the Barkhof scale (Barkhof et al. 2013) to assess the radiological severity of ARIA-E. In this study, the Sponsor plans to use the Bioclinica 5-point scale (Bracoud et al. 2017), which is a simpler scale for assessing ARIA-E severity that is based on a single overall assessment of ARIA-E extent. The Bioclinica 5-point scale is easier for clinicians to use than the Barkhof scale. The Bioclinica scale is commonly used in other clinical trials that are testing anti-amyloid antibodies (Ferrero et al. 2016).

Most cases of ARIA-E occur as an imaging finding alone, without any detectable clinical symptoms (see Gantenerumab Investigator's Brochure safety summary section). As detailed in Appendix 2, ongoing dosing of gantenerumab will occur in cases where ARIA-E is asymptomatic with a low or moderate imaging severity; in such cases, more frequent MRI surveillance (Q4W) will be mandatory. Any ARIA-E associated with symptoms (see definition of symptomatic ARIA-E in Section 5.3.5.2 and Appendix 2), regardless of radiographic severity, will require temporary withholding of study drug administration, until symptoms and ARIA-E findings resolve. The goal, in the context of this carefully controlled study with strict safety monitoring, is to minimize unnecessary study drug interruption, which could itself have a negative impact upon participants. Because of the safety monitoring and the regular review of safety data by the iDMC, this ARIA management strategy has a neutral impact upon participant risk.

3.3.5 Rationale for Biomarker Assessments

The following biomarker assessments will be used to investigate the effects of gantenerumab on the underlying pathology of AD in the participant population: CSF, plasma, and RNA (Section 4.5.7.3); PET imaging (Section 4.5.11); and brain volumetry, connectivity, and fiber tract integrity (Section 4.5.10).

Exploratory research on potential safety biomarkers may be conducted to support future drug development, including guidance for safety risk management.

3.3.5.1 Cerebral Spinal Fluid Biomarkers

Amyloid plaque deposition, neurofibrillary tangle formation, and neuronal degeneration are known pathologic features of AD. Decreased CSF $A\beta_{1-42}$ and elevated CSF t-tau

and p-tau are considered a biochemical signature of AD. Accumulating evidence suggests that low CSF $A\beta_{1-42}$ reflects underlying amyloid plaque pathology, whereas increased t-tau and p-tau levels may be reflective of neurodegeneration and/or tau pathology. Amyloid deposition may be the initiating event in the cascade of pathologic processes underlying AD, whereas tau pathology appears to be a subsequent event and more associated with neurodegeneration. Therefore, t-tau and p-tau may be studied as downstream biomarkers of the primary target of anti-amyloid therapies such as gantenerumab.

Although biomarkers indicative of certain neuropathologies have not yet been validated as surrogate markers for clinical efficacy, there is some evidence that anti-$A\beta$ treatments may cause changes in these biomarkers. A neuropathologic study of patients with AD (Study AN1792) suggests that active amyloid immunotherapy ameliorates neurite abnormalities and tau pathology through decreased tau phosphorylation (Serrano-Pozo et al. 2010). In a pooled analysis of CSF data from two Phase II trials with bapineuzumab in patients with mild to moderate AD, a decrease in both p-tau and t-tau levels relative to baseline was observed in the bapineuzumab group after 12 months of therapy (Blennow et al. 2010). These findings were confirmed in two Phase III studies with bapineuzumab (Sperling et al. 2012) as well as in Study WN25203 with gantenerumab. In Study WN25203, CSF biomarkers were analyzed over the 2-year period for changes in multiple proteins, including $A\beta_{1-42}$, t-tau, p-tau, and neurogranin. Markers of neurodegeneration were significantly reduced in the 225-mg gantenerumab group compared with placebo over 2 years, with greater relative reduction in p-tau relative to t-tau. The greatest effect was reduction in p-tau in the 225-mg gantenerumab arm at 2 years relative to the change in the placebo arm. There was no treatment effect on CSF $A\beta_{1-42}$ (Nikolcheva et al. 2015). Because no evidence of efficacy has been demonstrated with these therapies in clinical trials yet, changes in these biomarkers provide meaningful information about the PD effects of gantenerumab and the effect on pathologic processes underlying AD.

Based on these data and on the proposed mechanism of action of gantenerumab, levels of CSF t-tau and p-tau and additional exploratory biomarkers reflecting neurodegeneration will be assessed in this study. Because gantenerumab is expected to clear amyloid from the brain, levels of CSF $A\beta_{1-42}$ will also be measured.

3.3.5.2 Brain Volumetry, Connectivity, and Fiber Tract Integrity

A characteristic feature of AD is neuronal destruction. Such neuronal loss is demonstrated at a macroscopic level by progressive cerebral atrophy, which can be tracked on MRI (Fox and Kennedy 2009). Multiple changes in brain anatomy beyond those associated with normal aging have been reported in patients with AD (e.g., enlarged ventricles, decreased cortical thickness, decreased total brain volume, and hippocampal atrophy), and there is evidence for strong correlations between these imaging biomarkers and functional cognitive measures (Li and Wahlund 2011). Based

on volumetric MRI measurements, the two most established markers of disease progression in longitudinal observational studies are hippocampal and whole brain atrophy (Fox et al. 2000, 2005; Jack et al. 2010), with ventricular expansion a related quantitative marker.

Therefore, to quantify the effects of gantenerumab on neurodegeneration, whole brain volume, ventricular enlargement, and regional brain volume changes will be assessed in this study. All MRI reads and volume measures will be conducted by the central reader.

In addition to the structural brain volume changes, changes in brain functioning of participants will be assessed using a blood oxygenation level-dependent (BOLD) resting-state functional MRI (rs-fMRI) procedure (at sites where this procedure is available) with a paradigm-free procedure (Grecius et al. 2004; Filippi and Agosta 2011). Increased concentrations of Aβ in the brains of patients with AD contribute to neuronal degeneration in the brain over time and have been associated with reduced functional connectivity of various brain networks using rs-fMRI (Sheline et al. 2010; Binnewijzend et al. 2012; Brier et al. 2012; Sheline and Raichle 2013). Resting-state functional connectivity has been found to be decreased in brain regions such as the hippocampus, the default mode network (regions such as precuneus, anterior cingulate, and parietal and temporal cortices), and cortical regions in which the functional connectivity is continuously decreased as disease progresses. It has also been found to be decreased in cognitively normal elderly patients with brain amyloid deposition (Pittsburgh Compound-B+ PET scans). Alteration of the decreased brain functional connectivity has been shown using therapeutic interventions such as memantine (Lorenzi et al. 2011) or donepezil in patients with AD (Goveas et al. 2011; Solé-Padullés et al. 2013). Increased brain functional connectivity was found after just 3 months of treatment with donepezil, and this correlated with changes in cognitive measures such as the ADAS-Cog (Goveas et al. 2011; Solé-Padullés et al. 2013). Therefore, therapeutic interventions, which act to remove Aβ from the brains of patients with AD, may help to reverse the altered functional connectivity presumably caused by the accumulation of Aβ in the brain.

The integrity of white matter tracts will be assessed prior to and after treatment with gantenerumab using diffuse tensor imaging (DTI)-MRI techniques. DTI-MRI is based on the measurement of diffusion properties of water molecules in the axonal fiber tracts in white matter. Whereas water molecules can diffuse isotropically in CSF, they are restricted axially in white matter bundles. Widespread group differences in the degree of anisotropic diffusion, or fractional anisotropy (FA), has been seen between patients with AD and healthy subjects (Jack et al. 2015). Greater FA values are thought to indicate greater white matter integrity. Likewise, mean diffusivity, which measures the average rate of diffusion in all directions, has been shown to be higher in groups with AD compared with healthy controls, presumably owing to increased white matter injury in patients with AD (Nir et al. 2013).

At sites having the required software and hardware, rs-fMRI (BOLD rs-fMRI) and DTI-MRI will be performed when feasible during the same scanning session as the structural MRI to assess functional brain connectivity and fiber tract integrity.

3.3.6 Rationale for Pharmacokinetic Sampling

A sparse sampling schedule is being utilized to minimize participant burden while providing an adequate characterization of the population PK profile of gantenerumab. The PK data may be combined with available data from other gantenerumab studies and may be used to assess exposure–response relationships for relevant imaging, CSF, plasma PD biomarkers, ECGs, and efficacy and safety outcomes in participants with AD, as appropriate.

4. MATERIALS AND METHODS

4.1 PARTICIPANTS

Any participant who has completed Study WN29922 or WN39658, either the double-blind or OLE part, as applicable, can be enrolled in this study if they meet the inclusion/exclusion criteria set out below. This should lead to no more than 2032 participants with AD enrolled in WN42171, dependent on the number of eligible participants completing the parent studies and who consent to WN42171.

4.1.1 Inclusion Criteria

Participants must meet the following criteria for study entry:

- Signed Informed Consent Form by the participant with AD and/or the legal authorized representative as per local requirements
- Completed Study WN29922 or WN39658, either its double-blind part (participants have reached the 510 mg Q2W dose schedule by the time of completion) or OLE part (participants have received at least 3 doses of 510 mg Q4W), and did not discontinue study drug early
- Ability to comply with the study protocol
- Willingness and ability to complete all aspects of the study (including MRI and lumbar puncture [if applicable]).

  The participant should be capable of completing assessments either alone or with the help of the caregiver.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for at least 16 weeks after the final dose of gantenerumab.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not

permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.2 Exclusion Criteria

Participants who meet any of the following criteria will be excluded from study entry:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within at least 16 weeks after the final dose of study drug

  Women of childbearing potential must have a negative urine pregnancy test at the final visit of the parent study.
- Prematurely discontinued from Study WN29922 or WN39658, either its double-blind or OLE part, as applicable, or from study drug, for any reason
- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Received any investigational treatment other than gantenerumab during or since completion of Study WN29922 or WN39658, either its double-blind or OLE part, as applicable
- Evidence of disseminated leptomeningeal hemosiderosis (i.e., more than three focal leptomeningeal hemosiderosis)
- Evidence of intracerebral macrohemorrhage
- Use of prohibited medication (see Section 4.4.2)
- Evidence of ARIA-E on the last MRI scan report in Study WN29922 or WN39658, either its double-blind or OLE part, as applicable

  Participants should remain in the parent study, as governed by that protocol, and may enroll in this study once the ARIA-E is resolved.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a non-randomized, open-label study. An interactive voice or web-based response system (IxRS) will be used to manage participant enrollment and drug supply. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the patient's identification number and treatment assignment from the IxRS.

Participants randomized to the active treatment arm in the parent study will continue to be administered the study drug every 2 weeks (Q2W administration of 510 mg SC gantenerumab). Participants randomized to the placebo arm in the parent study will have to go through at least 34 weeks of uptitration. Participants, sites, and Sponsor will remain blinded to previous treatment allocation in the WN29922 or WN39658 studies to protect study integrity.

4.2.2 Blinding

Study site personnel and participants will be blinded to previous treatment assignment in the WN29922 or WN39658 studies. The Sponsor and its agents will also be blinded to previous treatment assignment, with the exception of individuals who require access to participant's treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, operational assay group personnel, IxRS service provider, and iDMC members.

PK and immunogenicity samples will be collected from all participants, regardless of the treatment assignment. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to participants' treatment assignments. Baseline immunogenicity samples will be analyzed for all participants.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which participant management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to participant unblinding, the investigator will be able to break the treatment codes by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment assignment code for all serious, unexpected suspected adverse

reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The participant may continue to receive treatment, and the investigator, participant, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to participant treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is gantenerumab.

4.3.1 Gantenerumab and Placebo

The Sponsor will supply gantenerumab and placebo, as required for the uptitration period, as liquid formulation ready for SC administration. Packaging of the study drug will be overseen by the Roche Clinical Trial Supplies Department and will bear a label with the identification required by local law, the protocol number, study drug identification, and dose. The packaging and labeling will be in accordance with Roche standard and local regulations. Upon receipt of the investigational products at the site, site personnel should check the product for damage and verify the proper identity, quantity, and integrity of the study drug. Site personnel should report any deviations or product complaints to the monitor upon discovery. For further details, please refer to the Gantenerumab Investigator's Brochure.

For information on the formulation and handling of gantenerumab, see the pharmacy manual and the Gantenerumab Investigator's Brochure.

4.3.2 Study Treatment Dosage, Administration, and Compliance

During the WN42171 study, participants previously randomized to the active treatment arm and those who were previously randomized to placebo and have completed OLE uptitration in WN29922 or WN39658 will continue to be administered the study drug every 2 weeks (Q2W administration of 510 mg SC gantenerumab). Participants previously randomized to the placebo arm who did not participate in the OLE part of the WN29922 or WN39658 study will be required to undergo the uptitration scheme of 34 weeks. Participants who completed the OLE part of the WN29922 or WN39658 study, will continue the schedule of activities as per their last visit in the OLE part of the parent study (WN29922 or WN39658).

In order to maintain the previous study treatment blinding (the Sponsor, Investigator, and participant), all participants will be dosed every 2 weeks as illustrated in Table 1. A safety MRI should be performed before each uptitration to ensure the participant can be safely uptitrated to the next dose.

To ensure blinding to previous treatment, IMP will be administered as one 0.8-mL and two 1.7-mL injections for the 120-mg dose or as two 1.7-mL injections for the 255-mg

dose and 510-mg dose, respectively, SC to the abdomen. Injections may contain active gantenerumab or placebo to ensure the correct total dose of active gantenerumab at each visit (see Table 1). Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Note: A minimum of 3 doses during each dosing step must be administered before the participant is eligible for uptitration, subject to the results of a pre-uptitration safety MRI. **A dose is defined as two consecutive dosing visits (one with an even dose number and one with an odd dose number, see Table 1).**

After OLE Week 34 (i.e., beyond the time frame considered in **Table 1**), all participants who have completer the uptitration will receive two 1.7-mL injections of active gantenerumab for the 510-mg dose at each subsequent 2-week visit.

At applicable sites, study treatment may be administered by a trained nursing professional at the participant's home or another suitable location, if the participant has given written informed consent to participate in home nursing visits.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error along with any associated adverse events should be reported as described in Section 5.3.5.13.

Guidelines for treatment interruption or discontinuation for participants who experience selected adverse events are provided in Section 5.

Table 1 Gantenerumab Dosing Design for Participants Who Did Not Participate in the OLE Part of the Parent Study (WN29922 or WN39658)

Visit		OLE Day 1	OLE Wk 2	OLE Wk 4	OLE Wk 6	OLE Wk 8	OLE Wk 10	OLE Wk 12	OLE Wk 14	OLE Wk 16	OLE Wk 18	OLE Wk 20	OLE Wk 22	OLE Wk 24	OLE Wk 26	OLE Wk 28	OLE Wk 30	OLE Wk 32	OLE Wk 34
Dose Number Within the WN42171 Study		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Participants previously on placebo	Dose	120 mg Q4W						255 mg Q4W							510 mg Q4W				
	Injections (mL)	1× 0.8A + 2× 1.7P	1× 0.8P + 2× 1.7P	1× 0.8A + 2× 1.7P	1× 0.8P + 2× 1.7P	1× 0.8A + 2× 1.7P	1× 0.8P + 2× 1.7P	1× 1.7A + 1× 1.7P	2 × 1.7P	1× 1.7A + 1× 1.7P	2× 1.7P	1× 1.7A + 1× 1.7P	2× 1.7P	2× 1.7A	2× 1.7P	2× 1.7A	2× 1.7P	2× 1.7A	2× 1.7P
Participants previously on active	Dose	510 mg Q2W																	
	Injections (mL)	2× 1.7A + 1× 0.8P	2x 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A

A = active treatment; OLE=open-label extension; P = placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; Wk = week.

4.3.3 PET Tracers

All participants who are enrolled in the PET substudies will be assessed by PET imaging using the same PET ligand as per the parent study (florbetaben or flutemetamol for the amyloid PET and [^{18}F]GTP1 for the tau PET substudy). According to E.U. guidance, the PET tracers, as used in the context of this study, are designated as non-IMP. In some regions, according to local regulations, these PET tracers may be considered to be IMP.

In countries where the PET radioligands are approved for marketing, the approved local product information will be provided, and in countries where they are not approved for marketing, the Investigator's Brochures will be provided.

For the safety reporting requirements dealing with the PET tracers used in this study please refer to Section 5.7.

4.3.4 Investigational Medicinal Product Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.5 Continued Access to Gantenerumab

The Sponsor will offer continued access to Roche IMP gantenerumab free of charge to eligible participants in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A participant will be eligible to receive Roche IMP gantenerumab after completing the study if all of the following conditions are met:

- The participant has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being.
- There are no appropriate alternative treatments available to the participant.
- The participant and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A participant will not be eligible to receive Roche IMP gantenerumab after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the participant's country and is reasonably accessible to the participant (e.g., is covered by the participant's insurance or wouldn't otherwise create a financial hardship for the participant).
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for AD.
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for AD
- Provision of the Roche IMP is not permitted under the laws and regulations of the participant's country.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a participant in addition to protocol-mandated treatment from 3 months prior to first administration of study drug in Study WN42171 to the OLE final follow-up visit. All concomitant medications used by the patient during the WN42171 study should be reported by the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Participants are eligible for study participation whether or not they are receiving approved medication for AD (i.e., AChEIs, memantine, and/or medical food supplements, where approved) with the exception of GV-971. Participants who have received GV-971, are currently receiving GV-971 or who are planning to receive GV-971 during the study are not eligible. Information about background AD medication (e.g., drug name, dose, and start and stop dates, reason for interruption or modification) should be captured on the eCRF.

Adding a new medication or changing the dose of a medication during the study should occur only for the treatment of an adverse event or in case of AD progression. Whenever possible, a medication listed below should be used if appropriate.

The following medications are permitted if the dose and dose regimen have been stable for at least 3 months prior to baseline and are expected to remain stable after baseline:

- Anticonvulsant medications for an approved pain indication
- Selective serotonin reuptake inhibitors for the treatment of depressive symptoms
- Over-the-counter and/or herbal medications, food additives, or any other agent or supplement intended to improve cognition or reduce cognitive decline

- Medications used to treat a mood or anxiety disorder given as maintenance treatment (with the exception of benzodiazepine)
- Intermittent use of short-acting (non-extended release) opioid medications for pain except within 2 days or 5 half-lives (whichever is the longer) of any cognitive assessment (up to a maximum of 3 consecutive days per month)
- Intermittent use of benzodiazepines, including alprazolam, lorazepam, oxazepam, triazolam, or temazepam, or a one-time dose of diazepam or a short–acting hypnotic medication (e.g., zolpidem) if use is intermittent for sleep or anxiety, except within 2 days or 5 half-lives (whichever is the longer) prior to any cognitive assessment
- A dose of benzodiazepine for pre-surgical and pre-imaging sedation at appropriate visits if allowed by the Ethics Committee (EC) or Institutional Review Board (IRB)
- Intermittent use of centrally acting antihistamine medications except within 2 days or 5 half-lives (whichever is the longer) prior to any cognitive assessment
- Under certain circumstances, initiation of anti-hemostasis medications during the study

Anticoagulation therapy lasting no longer than 3 weeks (e.g., temporary usage during surgery) is permitted. Nevertheless, no anticoagulation therapy should be initiated without discussion with and approval by the Medical Monitor.

Participants who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

4.4.2 Prohibited Therapy

The following medications are prohibited at study start and during the entire period of study participation. Participants who start these medications during the study may be withdrawn from study treatment:

- Any active immunotherapy (vaccine) that is being evaluated to prevent or postpone cognitive decline
- Any passive immunotherapy (immunoglobulin) or other long-acting biologic agent that is under evaluation to prevent or postpone cognitive decline within 1 year of screening, except for gantenerumab
- Any other investigational treatment or any other treatment with an investigational monoclonal antibody within 5 half-lives or 4 months prior to screening, whichever is longer
- Any previous administration of GV-971
- Anti-coagulation medications

  Anti-platelet treatments (e.g., aspirin, clopidogrel, and dipyridamol) are permitted.

  Short-term, perioperative use of anticoagulant medications will not result in permanent discontinuation from the study; however, any such use must be

discussed prospectively with the Medical Monitor and may require temporary study drug interruption.

The following medications will not be allowed in this study unless they were administered during the parent studies and/or they are used under certain rules:

- Medications specifically intended to treat Parkinson symptoms or any other neurodegenerative disorder;

  Certain medications are acceptable if the participant is taking the medicine for a non-neurodegenerative disorder, such as restless leg disorder (e.g., pramipexole)

- Stimulant medications (amphetamine, methylphenidate preparations, or modafinil) throughout the study
- Typical antipsychotic or neuroleptic medication, except as brief treatment for a non-psychiatric indication (e.g., emesis) or for intermittent short-term use

  They will need to be discontinued 2 days or at least 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

- Atypical antipsychotic medications are not allowed except for intermittent short-term use

  They will need to be discontinued 2 days or at least 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

- Chronic use of opiates or opioids (including long-acting opioid medication)

  Intermittent short-term use of short-acting opioid medications for pain is permitted except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

- Chronic use of benzodiazepines, barbiturates, or hypnotics

  Intermittent short-term use of benzodiazepines, buspirone, or short-acting hypnotic medication for sleep or anxiety is allowed except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each participant.

At applicable sites, certain study assessments may be performed by a mobile nursing (MN) professional at the participant's home or another suitable location, such as a nursing center, to improve access and convenience for participants participating in the study. The Sponsor will select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a participant and the participant gives written informed consent to

participate in MN visits, the MN network will communicate with the participant and the participant's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. The schedule of activities (see Appendix 1) specifies the assessments that may be performed by an MN professional.

4.5.1 Informed Consent Forms and Screening Log

Informed consent should be obtained while participants are still in the parent study until a day before the first dose in the study WN42171. In special situations, informed consent can be obtained at a later timepoint upon discussion with the Medical Monitor. Written informed consent for participation in the study must be obtained before performing any study-related procedures. Informed Consent Forms for enrolled participants and for participants who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be reviewed to confirm that participants meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Baseline Definition and Assessments

For participants who completed the double-blind part and did not enter the OLE part of Study WN29922 or WN39658: The first dosing visit in this study will be considered as baseline (OLE Day 1), and the Week 104 assessment of the parent study will be considered as baseline assessment if occurring within a specific timeframe.

For participants who completed the double-blind part and the OLE part of Study WN29922 or WN39658: The baseline visit will be the OLE Day 1 visit of the parent study (WN29922 or WN39658). This group of participants will roll over to the WN42171 study upon the completion of their uptitration. The first visit in this study should take place approximately 2 weeks after the OLE Week 34 visit or the last dose visit in the WN29922 or WN39658 OLE

On the day of the first dose of gantenerumab in Study WN42171, if results of standard-of-care tests or examinations (coagulation, ECG, serum chemistry, and hematology; complete physical examination) performed within 4 weeks are available, they do not have to be repeated. For C-SSRS, and cognitive scale results, the time interval is 6 months. MRI scan does not need to be repeated if performed within 6 months in the parent study and following the final study drug dose in the parent study. Vital signs, urine pregnancy test for women of childbearing potential, collection of adverse events, and review of concomitant medications have to take place before each dose administration. The MRI can only be used if it was the last prescribed per-protocol MRI in the parent study.

4.5.3 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history and demographic data as collected in the WN29922 or WN39658 parent study will be used in this study and should include clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse. Medical history and demographic data will be automatically transferred into the WN42171 eCRF. In addition, ongoing concomitant medications will automatically be transferred from the parent study to Study WN42171. All changes to medications during the study (e.g., prescription drugs, over the counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) should be recorded in the eCRF. Changes in medical history will be collected once after completion of the double-blind part in the parent study (WN29922 or WN39658) and before OLE Day 1 either in the parent study or in Study WN42171.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.4 Physical Examinations

A complete physical examination, performed at specified visits as per the schedule of activities (Appendix 1), should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated. Conditions reported as part of the medical history or adverse events in the parent study do not need to be re-entered.

Limited, symptom-directed physical examinations should be performed at specified visits and as clinically indicated. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

In addition, weight will be obtained at OLE Day 1, at OLE Week 104 or at the OLE early termination visit, at every visit at which creatinine clearance is tested, and at any other visit as deemed necessary by the investigator. Height will be obtained at the first dosing visit only.

The physical examination does not have to be repeated at OLE Day 1 or at the first dosing visit in the WN42171 study if the last examination performed in the parent study (WN29922 or WN39658) occurred within the previous 4 weeks.

4.5.5 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure while the participant is in a seated position, and temperature. Any abnormalities recorded in the parent studies do not need to be re-entered on the WN42171 eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements.

Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

Vital sign measurements may be performed by an MN professional.

4.5.6 Cognitive, Functional, and Health Economics Assessments

The assessments described in this section will be performed as outlined in the schedule of activities (see Appendix 1) and in the order specified in Section 4.5.6.14.

Whenever possible, there should be consistency in the rater and caregiver who complete the scales for each participant throughout the duration of this study and also between this study and the parent study. Potential raters will receive training and be approved by the rating scale contract research organization prior to being allowed to administer any cognitive assessments or rating scales in the study.

Whenever possible, cognitive and functional assessments should be performed at the visit timepoints indicated in the schedule of activities (see Appendix 1). However, in exceptional circumstances, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per the schedule of activities, they may be performed up to 4 weeks out of window.

Given that the secondary efficacy outcome measure in this trial, CDR, involves subjective judgment, the adequacy of participant and caregiver interviews and ratings will be monitored by an endpoint reliability program administered by the rating scale vendor. This is considered an essential part of good research methodology. For CDR as well as for some other scales, audio recordings may be used for quality assurance purposes. Prior studies have clearly demonstrated that the failure to adequately monitor such ratings can substantially increase the risks of failed trials (Becker and Greig 2008; Kobak 2010).

During OLE Day 1 or the visit of the first study drug administration in the WN42171 study, scale assessments do not have to be repeated if the last assessments performed in the parent study WN29922 or WN39658 occurred within 6 months.

4.5.6.1 Clinical Dementia Rating Scale

The CDR–Global Score (CDR-GS) characterizes a participant's level of impairment according to the following categories: 0 (normal), 0.5 (very mild dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia). The CDR–Sum of Boxes (CDR-SOB) score is a detailed quantitative general index that provides more information

than the CDR-GS in participants with mild dementia (Berg 1988; Morris et al. 2001, O'Bryant et al. 2010) and is scored from 0–18 with higher scores indicating greater impairment. The CDR characterizes six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The necessary information to make each rating is obtained through a semi-structured interview with the participant and a reliable informant or collateral source (e.g., a caregiver).

As much as is feasible, the CDR should be administered to an individual participant by the same assessor throughout the study, and that assessor should not perform the MMSE, ADAS-Cog, Verbal Fluency Task, Coding, FAQ, or ADCS-ADL. However, if in exceptional circumstances only this assessor is available to perform these other scales, then the CDR participant interview must be completed after the caregiver interview but before ADAS-Cog, MMSE, Verbal Fluency Task, Coding, and other scales are completed. Nevertheless, on OLE Day1, on OLE Week 52, and on OLE Week 104, the CDR rater cannot perform other scales than the CDR. In addition, the CDR rater should not be involved in safety assessments and especially should not receive information about any ARIA findings.

4.5.6.2 Alzheimer's Disease Assessment Scale−Cognitive Subscale

The ADAS-Cog is the most frequently used scale to assess cognition in clinical trials for mild to moderate AD dementia (Rozzini et al. 2007; Connor and Sabbagh 2008; Ihl et al. 2012). More specifically, the ADAS-Cog is a participant-based assessment that measures learning and memory, language production, language comprehension, constructional praxis, ideational praxis, and orientation. The modified version will be used; it has 13 items and includes the addition of delayed word recall and a number of cancellation subtests, as well as use of only one trial for word recognition (Mohs et al. 1997). Equivalent alternate forms of the word recall, word recognition, and number cancellation subtests will be used in successive test administrations.

4.5.6.3 Mini-Mental State Examination

The MMSE is a set of standardized questions used to evaluate possible cognitive impairment and help stage the severity level of this impairment (Folstein et al. 1975). The questions target six areas: orientation, registration, attention, short-term recall, language, and constructional praxis/visuospatial abilities. The MMSE is a participant-based assessment.

4.5.6.4 Verbal Fluency Task

The category verbal fluency (e.g., animals) is a participant-based assessment that measures speed and flexibility of verbal thought. Verbal fluency tests are sensitive tools for detecting dementia (Pasquier et al. 1995; Lezak et al. 2004) and for monitoring decline over time (Clark et al. 2009).

4.5.6.5 Coding

The Coding, also called Digit Symbol Substitution Test (or DSST), is a subtest from the Wechsler Adult Intelligence Scale−Fourth Edition (WAIS−IV; Wechsler 2008). The Coding is a participant-based assessment that measures speed of processing and associative memory. The test is known to be sensitive to disease progression (Lezak et al. 2004). The 120-second version of the test will be used in this study.

4.5.6.6 Functional Activities Questionnaire

The FAQ (Pfeffer et al. 1982) is an informant-based measure of functional abilities. Informants provide performance ratings of the target person on ten complex higher-order activities.

4.5.6.7 Alzheimer's Disease Cooperative Study−Activities of Daily Living Inventory

The ADCS-ADL (Galasko et al. 1997) is the scale most widely used to assess functional outcome in participants with AD (Vellas et al. 2008). The ADCS-ADL is a 23-item informant-based questionnaire that covers both basic activities of daily living (ADL) (e.g., eating and toileting) and more complex ADL or instrumental ADL (e.g., using the telephone, managing finances, preparing a meal). It has a 4-week recall period. Total scores range from 0−78, with higher scores indicating better functioning.

4.5.6.8 Zarit Caregiver Interview for Alzheimer's Disease

ZCI-AD is a modified version of the Zarit Burden Interview, which was originally designed to reflect the stresses experienced by caregivers for people with dementia (Zarit and Zarit 1990). The modified version includes slight modifications in item and title wording (e.g., removal of "your relative" to refer directly to the participant, removal of "burden" from title) and the use of 11-point numerical rating scales. The ZCI-AD scale consists of 30 items and is completed by the caregiver without involvement from the site staff. It has a 4-week recall period.

If a participant's caregiver is replaced during the study, the ZCI-AD will not be completed by his or her new caregiver.

4.5.6.9 Quality of Life–Alzheimer's Disease

The QoL-AD was developed to assess quality of life (QoL) in participants who have dementia (Logsdon et al. 1999, 2002). The QoL-AD consists of 13 items covering aspects of participants' relationships with friends and family, physical condition, mood, concerns about finances, and overall assessment of QoL. The total score is the sum of the 13 items and ranges from 13−52, with higher scores indicating better health-related QoL.

In this study, the QoL-AD will be administered in a standardized, structured interview format to participants by investigative staff in order to gather participant responses about QoL. The caregiver will also complete the caregiver version of the questionnaire to enable proxy responses from the caregiver.

4.5.6.10 EQ-5D

The EQ-5D is a standardized measure of health status designed to provide a simple generic measure of health for clinical and economic appraisal. It is broadly applicable across a wide range of health conditions and treatment.

The EQ-5D assesses five domains to provide a health state index. These are anxiety/depression, pain/discomfort, usual activities, mobility, and self-care.

The following two versions will be used in this study:

- EuroQoL-5-Dimension, 5-Level Questionnaire (EQ-5D-5L) Proxy, Version 1: The caregiver (the proxy) is asked to rate the participant's health-related QoL in his or her (the proxy's) opinion.
- EQ-5D-5L, Self-Complete Version: The caregiver is asked to rate his or her own health-related QoL.

4.5.6.11 Resource Utilization in Dementia Scale

The RUD scale (Wimo et al. 2003) aims to document formal and informal resource use in a clinical trial setting. The RUD-Lite captures the most important elements in dementia care: accommodation, informal care, hospitalizations, and community care services. Information on caregiver sociodemographics in addition to working status and effect on productivity will be collected. The amount of informal care will be collected according to three types of care: personal ADL, instrumental ADL, and supervision. Data on accommodation and temporary changes in accommodation during the last month and the duration of these will be collected according to four levels of accommodation: own home, intermediate forms of accommodation, dementia-specific residential accommodation, and nursing home. Resource utilization will be recorded as the number of nights spent in different types of hospital wards, the number of visits to the most common types of outpatient care, and the number of visits in community care services.

4.5.6.12 Neuropsychiatric Inventory Questionnaire

The NPI-Q (Kaufer et al. 2000) was developed to assess a wide range of behaviors encountered in patients with dementia, to provide a means of distinguishing severity of behavioral changes, and to facilitate rapid behavioral assessment through the use of screening questions. It is an informant-based instrument in which 12 behavioral domains are evaluated. The recall period is the past month, and severity scores range from 0–36, with higher scores indicating greater severity. The caregiver's distress portion of the scale will not be used in this study.

4.5.6.13 Electronic Assessment of Rating Scales

The following rating scales will be captured electronically and transferred to the database directly from the core laboratory: ADAS-Cog, Verbal Fluency Task, ADCS-ADL, CDR, MMSE, FAQ, QoL-AD, EQ-5D, RUD-Lite, NPI-Q, and CSSR-S.

4.5.6.14 Treatment Period Assessments

The recommended order of assessments and rating scales is as follows:

- Clinical assessments (e.g., CDR, MMSE, and ADAS-Cog), including all those that require caregiver input, should be completed before any invasive safety assessments.
- Vital sign measurements, physical examination, ECGs, blood draws for clinical laboratory assessments, PK, ADA, plasma biomarker sampling, and urine samples are recommended to be conducted following scale assessments and must be performed prior to study drug administration.

The recommended order of clinical assessments/rating scales at baseline is as follows:

Participant Assessments	Caregiver Assessments
1. ADAS-Cog13	1. CDR (caregiver input)
2. CDR (participant interview)	2. FAQ
10-min break (optional)	3. ADCS-ADL
3. MMSE	4. ZCI-AD
4. Coding	5. QoL-AD
5. Verbal Fluency Task	6. EQ-5D
10-min break (optional)	7. RUD-Lite
6. QoL-AD	8. NPI-Q
7. C-SSRS	

ADAS-Cog13 = Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living; CDR = Clinical Dementia Rating; C-SSRS = Columbia–Suicide Severity Rating Scale; EuroQol-5-Dimension Questionnaire; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; NPI-Q = Neuropsychiatric Inventory–Questionnaire; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; ZCI-AD = Zarit Caregiver Interview for Alzheimer's Disease.

If assessments are split over 2 days, all safety assessments must be performed on the same day as the study drug administration.

On each dosing day, after all assessments prior to dosing have been completed (see the schedule of activities in Appendix 1), gantenerumab and matching placebo where applicable during uptitration will be administered SC at room temperature.

For participants who completed the double-blind part and did not enter the OLE part of Study WN29922 or WN39658: Participants should be observed for a minimum of 2 hours for the first eight administrations. Starting at the ninth administration, participants should be observed for a minimum of 1 hour.

For participants who completed the double-blind part and the OLE part of Study WN29922 or WN39658: Participants should be observed for a minimum of 1 hour.

Participants should leave the study center after injections only if they appear to be tolerating the injections. When doses are to be administered remotely from the clinical sites, study drug administration may be performed only by qualified health care providers, as defined by local regulations, who must remain with the participants for a minimum of 1 hour after each injection and be equipped with rescue medications.

Rescue medications to treat anaphylactic and anaphylactoid reactions must be available at the site or at the dosing location for HN visits. Participants and their caregivers will be alerted to watch for signs of anaphylactic and anaphylactoid reactions and to contact the study center as soon as possible if any such signs are noted.

Visits at which the participant receives study drug may take place within ± 3 days of the protocol-specified date in the schedule of activities (Appendix 1). It is recommended not to administer more than 2 complete doses (i.e., 2×510 mg Q2W) within 28 days. At every visit, participants should return to the initial planned visit schedule defined as per the baseline visit (OLE Day 1).

All visits should be scheduled as close as possible to the exact day. It is preferred that all assessments for a visit be performed on the same day, but if necessary, assessments may be performed over more than one day. Preferably, all clinical scales and assessments should be performed on the same day. Study drug administration should be performed only after all assessments and rating scales for the participant have been completed.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent for analysis:

- Serum chemistry panel: AST, ALT, ALP, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, serum creatinine (and creatinine clearance calculated by the central laboratory). Hemoglobin A_{1c} (HbA_{1C}), glucose, insulin, C-reactive protein, folic acid, and vitamin B-12 will also be assessed according to the schedule of activities (Appendix 1).
- Coagulation: PT time
- Thyroid function testing: thyroid-stimulating hormone, thyroxine (T4), and free T4
- Lipids: cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides
- Hematology: WBC count, RBC count (with morphology), hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).
- Urinalysis

  At the OLE Day1 visit or at the visit of the first study drug administration in the WN42171 study, if deemed necessary by the investigator, urinalysis may be performed at the site by dipstick for blood, protein, glucose, and pH. Microscopic examination will be performed by the central laboratory if blood and/or protein results are positive or strongly positive.

- Urine pregnancy test:

  Urine pregnancy tests will be performed at each dosing visit (prior to dose administration) for women of childbearing potential (including those who have had a tubal ligation) and at the site for any other female participants if required by local regulations. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory.

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

During the OLE Day 1 visit or at the visit of the first study drug administration in the WN42171 study, the above laboratory assessments do not have to be repeated if the last assessments performed in the parent studies WN29922 or WN39658 occurred within 4 weeks.

4.5.7.1 Pharmacokinetic Samples

Plasma Samples

Blood samples will be collected to evaluate the pharmacokinetics of gantenerumab in plasma as noted in the schedule of activities (see Appendix 1).

An additional PK sample for the assessment of plasma concentrations of gantenerumab will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) once the site becomes aware of the occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria.

Samples will not be analyzed in real time but will be batched for analysis throughout the study.

Unused sample material may be used for the purpose of current gantenerumab assay improvement and for the quantification of specific gantenerumab glycan species.

Cerebrospinal Fluid Samples

For participants who were randomized in the WN29922 or WN39658 studies based on CSF Aβ and tau level results who are willing to perform lumbar puncture in the schedule of activities, an aliquot of CSF obtained by lumbar puncture, described in Section 4.5.6.4, will be allocated for the measurement of gantenerumab concentration. Unused sample material may also be used for the purposes of current assay improvement.

4.5.7.2 Plasma Samples for Immunogenicity Analysis

Blood samples will be collected to assess the possible development of ADAs in all participants as noted in the schedule of activities (see Appendix 1). Plasma samples will be analyzed for antibodies to gantenerumab.

Unused sample material may also be used for the purposes of current ADA assay improvement.

4.5.7.3 Biomarker Samples

Samples will be obtained from all participants and will be used for research purposes to identify dynamic biomarkers that may be predictive of response to treatment with gantenerumab (in terms of dose, safety, and tolerability) and will help to better understand the pathogenesis, course, and outcome of AD and related diseases.

For participants who consent to the optional Roche Research Biosample Repository (RBR), residual biomarker samples will be kept for future biomarker research (see Section 4.5.14).

Cerebrospinal Fluid and Serum Biomarkers

CSF samples and matching serum samples will be obtained from participants who were randomized in the WN29922 or WN39658 parent studies based on CSF Aβ and tau level results. CSF samples will be collected during the study at different timepoints for monitoring the levels of Aβ and tau as well as other CSF biomarkers.

The serum samples collected at every timepoint at which a CSF sample is collected may be used to determine parameters that allow the assessment of blood-brain barrier status and/or inflammatory processes in the brain, such as the CSF/serum albumin ratio, CSF/serum IgG and IgM indices, and oligoclonal bands. CSF and serum samples will be collected according to the schedule of activities (see Appendix 1).

Lumbar puncture will be performed by an individual who meets all local requirements and is proficient in the procedure. Lumbar puncture procedures and post–lumbar puncture care will be performed in accordance with local practice. CSF sampling should be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters. Procedures for processing the CSF samples can be found in the Sample Handling and Logistics Manual.

Approximately 12 mL of CSF will be collected at each timepoint. The sample will be divided into aliquots onsite and used for the following:

- Central measurement of CSF gantenerumab levels
- Analysis of biomarkers in CSF, including $A\beta_{1-42}$, t-tau, p-tau, and other exploratory CSF biomarkers

Samples may also be used to support the development of biomarker assays for diagnostic use.

Plasma Biomarkers

Plasma samples will be collected at different timepoints (see Appendix 1) from every participant who has consented to participate in the study. Samples will be used to evaluate exploratory plasma biomarkers in peripheral blood, which may include, but will not be limited to Aβ, tau, neurofilament, and neurogranin.

An additional plasma sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E).

RNA Biomarkers

Blood samples at different timepoints (see Appendix 1) will be obtained for RNA extraction from every participant who has consented to participate in the study, at OLE Day 1 and at the visit of the first study drug administration in the WN42171 study (only if an RNA sample has not been collected at Week 104 or during the OLE part of the parent studies WN29922 or WN39658) and at OLE Week 104 visit or OLE early termination visit of this study.

The sample may be used to evaluate clusterin messenger RNA and other exploratory genetic markers in peripheral blood.

Additionally an RNA blood sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E).

SAMPLING PROCEDURES AND STORAGE

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Roche may keep information about test results, medical history, and demographic information for all participants also from the parent studies for future development of diagnostic tests related to Aβ, *APOE* genotype, and AD, as well as additional analyses.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (Section 4.5.14), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Plasma samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation, therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood, plasma, serum, and CSF samples collected for biomarker research and biomarker assay development will be destroyed no later than 5 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements)

When a participant withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the participant specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.8 Electrocardiograms

Single 12-lead ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

The centrally provided electrocardiograph machine should record the following: heart rate, QRS duration, and RR, PR, and QT intervals and transferred to the Sponsor database from the core laboratory.

At the OLE Day 1 visit or at the visit of the first study drug administration in Study WN42171, ECG does not have to be repeated if the last ECG performed in the parent studies WN29922 or WN39658 occurred within 4 weeks.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the participant has been resting in a supine position for at least 5 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws, brain MRI scans, and lumbar puncture). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site.

4.5.9 Columbia–Suicide Severity Rating Scale

The C-SSRS (http://www.cssrs.columbia.edu) is an assessment tool used to assess the lifetime suicidality of a participant (C-SSRS at baseline) as well as any new instances of suicidality (C-SSRS since last visit). The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual or potential lethality. The C-SSRS baseline from the parent study will be used, and the C-SSRS since the last visit will be collected at subsequent visits as indicated in the schedule of activities (see Appendix 1).

The assessment will be completed by a certified C-SSRS rater after he or she interviews the participant and the participant's caregiver during the study visit.

4.5.10 Brain Magnetic Resonance Imaging

MRI should be performed using 1.5-T or 3.0-T scanners. Whenever possible, the same scanner should be used for an individual participant for the full duration of the study. The MRI obtained at baseline and/or at Week 104 in the parent study may be used as a baseline measure of structural brain volumes and as baseline information for the PET substudies (see the schedule of activities in Appendix 1).

Where available, exploratory MRI techniques including rs-fMRI and DTI, will also be used.

The Week 104 MRI from the parent study will be used to determine whether there are any significant findings (e.g., presence of mass lesions, etc.) that may preclude the participant's safe participation in and completion of this study. Similarly, the MRI obtained at the end of the titration in participants who completed the parent study OLE will be used to determine if any significant findings preclude participation in the WN42171. In case of an ARIA-E finding, the participant should undergo Q4W MRI monitoring until the ARIA-E is resolved. Participants may enroll in study WN42171 once the ARIA-E is resolved.

MRI will be used during the study to help assess safety, such as the occurrence of ARIA. Additional unscheduled MRI scans may be performed to better understand if relevant CNS adverse events (such as increased confusion) are occurring in the context of ARIA or to follow up a sign that emerges at a scheduled scan; contrast agent may be used in such a case of follow-up MRI scans if administration of contrast agent is considered safe for the participant according to local standards. In addition, structural MRI (to assess whole brain and regional brain atrophy), fMRI, and DTI-MRI will be performed at multiple timepoints to determine potential treatment effects on MRI outcome measures (according to the schedule of activities).

MRI scans will include the following sequences:

- 3D T_1-weighted gradient recalled echo (GRE) scans
- T_2*-weighted GRE scans
- T_2-weighted fluid-attenuated inversion recovery scans
- BOLD rs-fMRI, if available (to assess resting-state functional connectivity at investigative sites having the required software and sequences)
- DTI-MRI, if available (to assess fiber tract integrity)

For details on the specific imaging sequences and acquisition times required, refer to the MRI manual.

MRI should not be performed unless at least 3 days have passed since a lumbar puncture. If an MRI and lumbar puncture are both scheduled for the same day, the MRI should be performed first.

MRI scans will be reviewed by a central MRI core laboratory, which will perform the diagnostic reads and assessments of MRI outcome measures. MRI scans should preferably be transferred to the central MRI core laboratory electronically. Data transfer from individual study sites to the central MRI core laboratory may take up to 7−10 days, if not done electronically. Upon receipt of the MRI scans from the study sites, the central MRI core laboratory will provide the diagnostic reads. MRI results must be made available to investigators prior to next dosing (refer to Section 5.1.2 for additional details on MRI safety management).

MRI facility qualification and scan quality control will be performed by the central MRI core laboratory.

In addition to any local reading according to local procedures and requirements, all MRI scans will be reviewed by an expert central reader within approximately 1 week of receipt and a report provided to the site. For the purposes of overall study relevant decisions and recommendations results from the expert central reader will be used. Any time the central reader identifies a new MRI finding, the study center medical staff and the Sponsor will be rapidly notified (see Section 5.1.2).

Refer to Section 5.1.2 for instructions in the event of new MRI findings (ARIA-E and ARIA-H).

At the OLE Day 1 visit or at the visit of the first study drug administration in the WN42171 study, MRI does not have to be repeated if the last MRI performed in the parent studies WN29922 or WN39658 is within 6 months. The MRI can only be used if it was the last prescribed per-protocol MRI in the parent study.

Additional instructions regarding the procedures for MRI scan acquisition and transmittal to the central reading facility can be found in the MRI manual.

Healthy Volunteer Magnetic Resonance Imaging Scans for Site Qualification

In case of a major upgrade to the site's scanner, any other event deemed significant enough to affect image quality, or per central reader guidance, the two volunteers will be asked to complete additional scans that will be reviewed for suitable image quality and used for qualitative comparison. The volunteer must provide written consent to take part in the scanning calibration. Volunteers must not have any contraindications for MRI scanning (evaluation per local procedures at the imaging site), and they will not be enrolled in the study or undergo any other assessments as part of the trial. This procedure will help ensure consistency in scanning quality over the duration of the study. Two volunteers are ideal in case one volunteer is no longer readily available for test scanning.

Additional instructions regarding the procedures for MRI facility qualification can be found in the MRI manual.

4.5.11 Positron Emission Tomography Scan

A PET scan will be performed in the context of the two associated PET substudies (a longitudinal amyloid PET substudy and a longitudinal tau PET substudy (see Section 3.1.2).

Detailed instructions regarding the procedures for PET scan methodology, including scanning procedures, can be found in the PET Technical Operations Manual.

4.5.12 Final Safety and Efficacy Visit Assessments

Participants who complete the treatment period (defined as completion of OLE Week 102 dosing visit) have to complete the final safety and efficacy assessment period 2 weeks following the final dose (Week 104).

4.5.13 Study Completion or Early Termination Visit Assessments

All participants who withdraw from treatment or discontinue from the study early will be asked to return 2 weeks after the final dose of study drug in order to complete the early termination visit.

In addition, participants who withdraw from treatment will be asked to return for collection of safety (except MRI) and limited efficacy data (i.e., secondary endpoints) at visits that have efficacy assessments (e.g., OLE Week 52, OLE Week 76, OLE Week 104, and OLE Week 116).

Autopsy reports, including cause of death, for all participants who die during the study (i.e., prior to the OLE Week 116 follow-up visit) should be requested.

Refer to the schedule of activities to be performed at the study completion (OLE Week 104 or OLE early termination visit) in Appendix 1.

When participants complete the treatment period or discontinue early, every effort should be made to ensure that the safety follow-up period and all related assessments are completed.

4.5.14 Optional Samples for Research Biosample Repository

4.5.14.1 Overview of the Research Biosample Repository

The RBR is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for participants in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.14.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.14) will not be applicable at that site.

4.5.14.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to gantenerumab, AD, or drug safety:

- Leftover blood, serum, plasma, CSF samples collected for biomarker analysis, and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which participants are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.14.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Participant medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.14.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a participant's agreement to provide optional RBR samples. Participants who decline to participate will not provide a separate signature.

The investigator should document whether or not the participant has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.14.6 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the participant. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a participant wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the participant's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a participant wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and participant number to the following email address:

global_rcr-withdrawal@roche.com

A participant's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a participant's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.14.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to participant participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits,

IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PARTICIPANT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Participants must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant
- Pregnancy
- Evidence of an intracerebral macrohemorrhage
- Evidence of disseminated leptomeningeal hemosiderosis

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue study treatment prematurely will not be replaced.

All participants who withdraw from treatment will be asked to return 2 weeks after their final dose in order to complete the early termination visit assessments.

In addition, participants who withdraw from treatment will be asked to return for collection of safety data (except MRI) and limited efficacy data (i.e., secondary endpoints) at visits that have efficacy assessments (e.g. OLE Week 52, OLE Week 76, OLE Week 104, OLE Week116) according to the schedule of activities.

4.6.2 Participant Discontinuation from the Study

Participants will return to the clinic for an early termination visit 2 weeks after last dose.

Participants have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a participant from the study at any time.

Reasons for participant discontinuation from the study may include, but are not limited to, the following:

- Participant withdrawal of consent
- Study termination or site closure
- Adverse event or any medical condition that the investigator or Sponsor determines may jeopardize the participant’s safety if he or she continues in the study
- Loss to follow-up

- Investigator or Sponsor determines it is in the best interest of the participant
- Participant non-compliance with the study and/or study procedures, defined as missing more than six consecutive dose administrations because of non–safety-related reasons or more than half of the dosing visits in a calendar year

Every effort should be made to obtain a reason for participant discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Participants who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.
- Data from other studies suggest that treatment with gantenerumab is likely not effective.
- Sponsor determines it is the best interest of the participants.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all participants have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Gantenerumab is not yet approved, and clinical development is ongoing. The safety plan for participants in this study is based on clinical experience with gantenerumab in completed and ongoing studies. The identified risks for gantenerumab are outlined below. Please refer to the Gantenerumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of participants participating in this study. Eligibility and discontinuation criteria both in the parent studies and in the WN42171 study have been designed to exclude participants at higher risk for imaging-related abnormalities. Participants will undergo safety monitoring during the study, including assessment of the nature, frequency, severity, and timing of adverse events. In addition, guidelines for managing selected adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Gantenerumab

5.1.1.1 Amyloid-Related Imaging Abnormalities

To date, clinical experience with gantenerumab has shown that ARIA events are dose- and *APOE* ε4-dependent. These events are manageable with MRI monitoring and dose intervention algorithms. In addition, in case of clinical symptoms, the use of IV glucocorticosteroids may be considered.

Rules for management of participants who develop ARIA-E or ARIA-H are provided in Appendix 2.

5.1.1.2 Injection-Site Reactions

Gantenerumab may cause a reaction when given as an SC injection. In studies with gantenerumab, the most common events occurring more frequently with gantenerumab than with placebo were local ISRs, such as injection-site erythema. The majority of events were of mild intensity and resolved without treatment (see Section 1.3.2.2 for details).

Detailed information on the characteristic signs and symptoms of ISRs (e.g., erythema, pruritus) will be recorded on the dedicated eCRF page (see Section 5.3.5.1 for details on recording of ISRs).

5.1.1.3 Immunogenicity

As with administration of any exogenous protein, there is the potential for the development of ADAs, which can be neutralizing and/or sensitizing and which can potentially lead to febrile or allergic reactions, including anaphylaxis. The immunogenic risk of gantenerumab is considered low since it is a fully human antibody.

There are no clinical findings indicative of an immunogenic response to gantenerumab. Investigators should explain to participants how to recognize the signs and symptoms of hypersensitivity reactions, and participants should be monitored.

5.1.2 Management of Participants Who Experience Adverse Events

5.1.2.1 Dose Modifications and Treatment Interruptions

Participants who completed the double-blind part and did not enter the OLE part of Study WN29922 or WN39658 will undergo uptitration in this study, which will last at least 34 weeks. During the uptitration phase, participants will undergo brain MRI

examinations prior to every dose increase (pre-uptitration MRI scans). The pre-uptitration MRI scans will determine eligibility for the next uptitration dose, as described in Appendix 2.

In order to determine the radiological severity of an ARIA-E event, the Bioclinica 5-point scale (Bracoud et al. 2017) will be used; refer to Table 2.

Table 2 Bioclinica 5-Point Scale Definition

ARIA-E Extent	ARIA-E Focality	5-Point Scale
No ARIA-E	N/A	0
< 5 cm	Monofocal	1 (Mild)
	Multifocal	2 (Mild +)
5–10 cm	Monofocal	3 (Moderate)
	Multifocal	4 (Moderate +)
> 10 cm	Monofocal	5 (Severe)
	Multifocal	

ARIA-E=amyloid-related imaging abnormality–edema/effusion; N/A=not applicable.

The participants' eligibility for uptitration will be determined according to the ARIA management rules outlined in Appendix 2. In the WN42171 study, there must be a minimum of 3 complete administrations of each dosing level for the participants to be eligible for a pre-uptitration MRI scan. A complete IMP administration is defined as two consecutive dosing visits (one with an even dose number and one with an odd dose number (see Appendix 1 and Appendix 2).

All participants, regardless of where they completed their gantenerumab dose uptitration (i.e., WN22992 or WN39658 OLE or this study), will undergo regular MRI scans according to the schedule of activities while they are on the target gantenerumab dose.

In addition, the dose adjustment and discontinuation rules for MRI findings as described in Appendix 2 will apply.

The investigator may choose to perform additional MRI monitoring for ARIA at any time. MRI monitoring of ARIA findings should be conducted at approximately 4-week intervals. Any other new significant findings will be reviewed by the Medical Monitor, and appropriate dose action will be taken.

The iDMC will review the incidence of ARIA in an unblinded manner and may recommend adjustment of dosing regimen and/or ARIA management rules for the overall study population or for a specific *APOE* ε4 genotype.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol–specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.10 and 5.3.5.11 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the participant at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.12)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the participant's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.8).
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.2.4 Selected Adverse Events

Additional data and safety MRI scans will be collected for the following selected adverse events:

- ARIA-E: ARIAs suggestive of vasogenic edema and sulcal effusions

- ARIA-H: ARIAs suggestive of microhemorrhages and/or hemosiderin deposits

Please refer also to Section 5.3.5.2 for further details how to report ARIA events.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4–5.6. The investigator is also responsible for reporting medical device complaints (see Section 5.4.4).

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each participant contact. All adverse events, whether reported by the participant, caregiver, or noted by study personnel, will be recorded in the participant's medical record and on the Adverse Event eCRF.

After informed consent has been obtained, all adverse events will be reported until the participant's final visit (including long-term follow-up visits).

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all participant evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

Table 3 provides guidance for assessing adverse event severity.

Table 3 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection-Site Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug injection should be captured as a diagnosis (e.g., "injection-site reaction" on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Injection Reaction eCRF. If a participant experiences both a local and

systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Reaction eCRF.

5.3.5.2 ARIA Findings

Not every ARIA finding qualifies as an adverse event. An ARIA finding must be reported as an adverse event if it meets any of the following criteria:

- Symptomatic ARIA-E (onset or worsening of CNS symptom[s] attributable to ARIA-E MRI findings in the judgement of the investigator)
- ARIA findings that result in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Findings that are otherwise clinically significant in the investigator's judgment

Any accompanying symptom(s) should also be captured as separate adverse events. It is the investigator's responsibility to review all ARIA findings. Observations of the same clinically significant ARIA finding should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.3 Diagnosis versus Signs and Symptoms

For adverse events other than ISRs or ARIA (see Sections 5.3.5.1 and 5.3.5.2, respectively), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.4 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.

- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.5 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.6 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN [upper limit of normal] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a

descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.7 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.8 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.3)

and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.9 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of AD.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of AD, “Alzheimer’s disease progression” should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.10 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for the parent study and at the beginning of this study. Conditions reported on the General Medical History eCRF in the parent study do not need to be re-entered. They will be reassessed if they are ongoing at the beginning of this study.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.11 Lack of Efficacy or Worsening of Alzheimer's Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.12 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The participant has not experienced an adverse event

5.3.5.13 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills

seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For gantenerumab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with gantenerumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the participant: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries

5.3.5.14 Clinical Outcome Assessment Data

Adverse event reports will not be derived from clinical outcome assessment (COA) data by the Sponsor, and safety analyses will not be performed using COA data. Sites are not expected to review the COA data for adverse events.

5.3.5.15 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2) for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2) for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

- Medical device complaints (see Section 5.4.4 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Contact Information for All Sites

Medical Monitor: [redacted] (Primary)

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Medical Monitor: [redacted], M.D., Ph.D. (Secondary)

Mobile Telephone No.: [redacted]

To ensure the safety of study participants, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the

event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until the participant's final visit (including long-term follow-up visits). Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Participants

Female participants of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 16 weeks after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF,

and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2. A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female participant exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 Reporting Requirements for Medical Device Complaints

The investigator must report all medical device complaints (e.g., devices for study drug administration) to the Sponsor. The investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the pharmacy manual for further details). If the medical device results in an adverse event to the study participant, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

5.5 FOLLOW-UP OF PARTICIPANTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the participant is lost to follow-up, or the participant withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as participant's final visit) if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Gantenerumab	Gantenerumab Investigator's Brochure
Florbetaben [^{18}F] (Neuraceq™)	Florbetaben [^{18}F] Investigator's Brochure
Flutemetamol [^{18}F] (Vizamyl™)	Flutemetamol [^{18}F] Investigator's Brochure
[^{18}F] GTP1	[^{18}F] GTP1 Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The purpose of this study is to assess the safety, tolerability, and efficacy of long-term administration of open-label gantenerumab in participants with AD who completed Study WN29922 or WN39658.

Data from OLE baseline (see Section 4.5.2 for definition) to the end of study will be summarized. Consequently, where appropriate, data from the parent studies will be combined with data from this protocol.

6.1 DETERMINATION OF SAMPLE SIZE

The sample size will include all eligible participants who consent to this study. The sample size is expected to be no more than approximately 2032 participants but will be determined by the number of participants who complete the WN29922 and WN39658 studies and enroll in this study.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, participant disposition, and incidence of protocol deviations will be summarized using descriptive statistics for all enrolled participants.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (such as age, sex, race, disease stage, *APOE* ε4 status, and use and non-use of background therapy for AD) will be summarized descriptively for all enrolled participants.

Descriptive summaries of continuous data will present the mean, standard deviation, median, and minimum and maximum. Descriptive summaries of discrete data will include frequencies expressed in terms of number and percentage of participants.

6.4 SAFETY ANALYSES

The safety analysis population will include all enrolled participants who received at least one dose of study drug in this protocol.

The following safety outcome measures will be summarized using descriptive statistics:

- Nature, frequency, severity, timing, and outcomes of adverse events and serious adverse events
- Physical examinations (including neurological systems), vital signs, blood tests, and C-SSRS
- Nature, frequency, severity, and timing of ARIA-E and ARIA-H

- Nature, frequency, severity, timing, and outcomes of injection-site reactions
- Incidence of treatment discontinuations for adverse events
- Incidence of adverse events of special interest

Statistical methods, endpoint definitions, and analyses of the safety endpoints will be described in the SAP.

6.5 EFFICACY ANALYSES

The secondary and exploratory efficacy analyses will use all enrolled participants to investigate both the long-term efficacy and potential disease modifying effect of long-term gantenerumab. Associated estimands, including those pertaining to a delayed start analysis, will be described in detail in the Statistical Analysis Plan (SAP). The efficacy endpoints collected during both the double-blind and OLE parts of the parent study (WN29922 or WN39658) may be combined with data from this study in order to evaluate the long-term effect of gantenerumab.

6.6 PHARMACOKINETIC ANALYSES

Plasma concentration data for gantenerumab will be tabulated and summarized. Descriptive summary statistics will include the arithmetic mean, median, range, standard deviation, and coefficient of variation, as appropriate. Because a sparse PK sampling design is being used, population (non-linear mixed-effects) modeling will be used to analyze the dose concentration–time data of gantenerumab. Information from other clinical studies may be incorporated to establish the PK model. The selection of parameters and the derivation of individual measures of exposure, such as area under the concentration–time curve, C_{max}, and trough plasma concentration, will depend on the final PK model used for this analysis. The results of this modeling analysis may be reported separately from the clinical study report. CSF concentrations of gantenerumab will be tabulated and summarized as appropriate.

Additional PK analyses will be conducted as appropriate and may be reported separately from the clinical study report.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all participants with at least one ADA assessment. The numbers and proportions of ADA-positive participants and ADA-negative participants prior to OLE drug administration and after OLE drug administration will be summarized using descriptive statistics.

6.8 BIOMARKER ANALYSES

PD and exploratory biomarker endpoints will be analyzed using descriptive statistics, subgroup analysis, or statistical models if appropriate. For longitudinally measured endpoints, the change from baseline will be estimated if appropriate. Exploratory biomarkers may be reported separately.

6.9 HEALTH STATUS UTILITY ANALYSES

Change over time in EQ-5D health utility index-based will be calculated. EQ-5D will be summarized using descriptive statistics. Details will be provided in SAP. EQ-5D will be used to estimate health state utility values needed for economic modeling. Such analyses will be reported separately.

6.10 INTERIM ANALYSES

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one or more interim efficacy analysis(es). An interim analysis may be considered when the parent pivotal studies WN29922 and WN39658 are completed and the submission folder is under preparation. Details will be pre-specified in the SAP.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. All electronic data from external vendors will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

COA data will be collected through the use of an electronic device (tablet) provided by a vendor (see Section 7.3 for details. Some COA data may be audio recorded for quality assurance purposes. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR, Part 11).
The electronic data are available for view access only via secure access to an online web portal. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor’s standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. The eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive participant data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 ELECTRONIC REPORTED OUTCOME DATA

An electronic device will be used by participants, caregivers, and appropriate site staff to capture COA data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with FDA regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure online web portal. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive participant data for the site in both human- and machine-readable formats that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participant-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays,

participant files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper COA data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each participant the objectives, methods, and potential risks associated with each optional procedure. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a participant's agreement to participate in optional procedures. Participants who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the participant or the participant's legally authorized representative before his or her participation in the study. The case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the participant to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a participant is participating in the study, the participant or a legally authorized

representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the participant or the participant's legally authorized representative. All signed and dated Consent Forms must remain in each participant's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include participant authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for participant authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the participant, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each participant enrolled in the study through assignment of a unique patient identification number. This means that participant names are not included in data sets that are transmitted to any Sponsor location.

Participant medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Medical information may be given to a participant's personal physician or other appropriate medical personnel responsible for the participant's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive

the participant data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring participant safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, participants' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

The overall procedures for quality assurance of clinical study data are described in Roche standard operating procedures. This study will be sponsored by F. Hoffmann-La Roche Ltd. Roche will provide clinical operations oversight, site monitoring and management, data management support, and medical monitoring.

Study drug distribution may occur through an IxRS (see Section 4.2). Central facilities may be used for study assessments (i.e., ECG, lumbar puncture, specified laboratory tests, PK, rating scales, and MRI and PET imaging), as applicable.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in participants involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in participants involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to participants or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

Table 1 Schedule of Activities for Participants Who Did Not Participate in the OLE Part of Parent Study WN29922 or WN39658

Assessment/Procedure	Screening	BL		OLE (week)																	UV[a]
	While in parent study to -1	OLE Day 1	OLE Day 4	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	
Dose number in the WN42171 study		1 [b]		2	3	4	5	6	7	8	9 [c]	10 [c]	11 [c]	12 [c]	13 [d]	14 [c]	15 [c]	16 [c]	17 [c]	18 [c]	
Dose level for participants previously on active		510 mg Q2W																			
Dose level for participants previously on placebo		120 mg							255 mg						510 mg						
Informed consent(s)	x																				
Review of inclusion and exclusion criteria		B																			
Medical history, personal status, and demographic data	x																				
Weight and height [e]		x													x						x
Clinical RNA samples		x [b]																			x
Urinalysis		x																			
Coagulation (PT)		B [b]																			
12-Lead ECG		B [b]																			x
Plasma PK sample [f]		B	x												x						x
Plasma ADA sample		B													x						x

Appendix 1: Schedule of Activities

Assessment/Procedure	Screening	BL		OLE (week)																	UV[a]
	While in parent study to -1	OLE Day 1	OLE Day 4	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	
Dose number in the WN42171 study		1 [b]		2	3	4	5	6	7	8	9 [c]	10 [c]	11 [c]	12 [c]	13 [d]	14 [c]	15 [c]	16 [c]	17 [c]	18 [c]	
Dose level for participants previously on active		510 mg Q2W																			
Dose level for participants previously on placebo		120 mg							255 mg						510 mg						
Serum chemistry [g] and hematology [h]		B [b]													x						x
Plasma biomarker sample		x [b]													x						x
Complete physical examination (includes neurologic systems) [i]		x [b]																			x
Limited physical examination [j]															x						x
MRI scan [k]		x [b, l]							x						x						x
CSF and matching serum samples [m]		x [b]																			
CDR		P& CG [b]													P& CG						P& CG
ADAS-Cog13		P [b]													P						P
Verbal Fluency Task		P [b]													P						P
Coding		P [b]													P						P
ADCS-ADL		CG [b]													CG						CG

Appendix 1: Schedule of Activities

Assessment/Procedure	Screening	BL		OLE (week)																	UV[a]
	While in parent study to -1	OLE Day 1	OLE Day 4	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	
Dose number in the WN42171 study		1 [b]		2	3	4	5	6	7	8	9 [c]	10 [c]	11 [c]	12 [c]	13 [d]	14 [c]	15 [c]	16 [c]	17 [c]	18 [c]	
Dose level for participants previously on active		510 mg Q2W																			
Dose level for participants previously on placebo		120 mg							255 mg						510 mg						
FAQ		CG [b]													CG						CG
MMSE		P [b]													P						P
EQ-5D		CG [b]													CG						CG
QoL-AD		P& CG [b]													P& CG						P& CG
ZCI-AD		CG [b]													CG						CG
RUD-Lite		CG [b]													CG						CG
NPI-Q		CG [b]													CG						CG
C-SSRS SLV		P [b]													P						P
Vital signs [n]		B	x	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [o]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [p]		B		B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	
Study drug administration [q]		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

Appendix 1: Schedule of Activities

Aβ=amyloid beta; ADA=anti-drug antibody; ADAS-Cog13 = Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer's Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormality–edema/effusion; ARIA-H = amyloid-related imaging abnormality–microhemorrhage/hemosiderin deposition; BL=baseline; CDR = Clinical Dementia Rating; CSF = cerebrospinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol 5-Dimension Questionnaire; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory Questionnaire; OLE = open-label extension; PK = pharmacokinetic; Q2W = every 2 weeks; QoL–AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SLV = since last visit; T4 = thyroxine; UV = unscheduled visit; ZCI-AD = Zarit Caregiver Interview for Alzheimer's Disease.

B = before study drug administration; P = participant completion; P&CG = participant and caregiver completion; CG = caregiver completion

Notes: The participant, the site, and the Sponsor will be kept blinded to the dose level given in order to keep the previous treatment assignment blinded. The visit window is ± 3 days and +3 days for OLE non-dosing Day 4. It is recommended that not more than 2 complete doses are given (i.e., 2 × 510 mg Q2W) within 28 days. Participants should return to initial planned schedule per baseline visit (OLE Day 1) for subsequent visits.

[a] The relevant assessments will be determined by the Principal Investigator per clinical judgment, not necessary to include all assessments listed above. An additional plasma and RNA blood sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E); following new or worsened ARIA-E.

[b] Results of standard-of-care tests or examinations (coagulation, ECG, serum chemistry, and hematology; complete physical examination) performed within 4 weeks prior to Day 1 may be used. MRI, C-SSRS, and cognitive scale results may be used if they have been performed within 6 months prior to OLE Day 1. If a clinical RNA sample or plasma biomarker or CSF and matching serum sample (where applicable) was collected at visit Week 104 of the parent study, another one does not have to be collected.

[c] At applicable sites, administration of gantenerumab may be performed by a mobile nursing professional at the participant's home or another suitable location, such as a nursing center, to improve access and convenience for participants participating in the study.

[d] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vital signs, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per the schedule of activities, they may be performed up to 4 weeks out of window.

[e] Height will be assessed only at the first dosing visit in the WN42171 study.

[f] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as soon as practicable (e.g., at an unscheduled visit or the next study visit) following a MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria (e.g., during an unscheduled visit).

[g] Serum chemistry includes AST, ALT, ALP, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). Hemoglobin A_{1c}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after a meal.

[h] Hematology includes WBC count, RBC count (with morphology), hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[i] A complete physical examination, performed at specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated.

[j] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[k] MRI must be performed at least 7 days before dosing, and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[l] Includes resting-state functional MRI and DTI outcome measures, where available.

[m] Lumbar puncture will be performed only in participants who were randomized in the WN29922 or WN39658 studies based on CSF Aβ and tau level results. It must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing (if applicable).

[n] Vital signs include measurements of pulse rate, respiratory rate, systolic and diastolic blood pressure while the participant is in a seated position, and temperature. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[o] After informed consent has been obtained, all adverse events will be reported until the participant's final visit (including long-term follow-up visits).

[p] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[q] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by SC injection (full details are provided in the pharmacy manual). Participants should be observed for at least 2 hours after the first 8 doses. From the ninth dose, this observation time may be reduced to 1 hour. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

Table 2 Schedule of Activities for Participants Who Have Completed Uptitration in Study WN42171 (continuation of Table 1)

Assessment/Procedure	Treatment Period										Final Safety and Efficacy Assess.	Follow-Up Period	Early Term. Visit	UV [a]
	OLE (week)													
Study schedule	36	38	40	41	42–50 [b]	52 [c]	54–74 [b]	76 [c]	78–102 [b]	103	104 [c]	116		
Dose number in the WN42171 study	19	20	21		22–26	28	29–39	40	42–53					
Dose level in milligrams (mg)	510 Q2W													
Weight						x		x			x	x	x	x
Clinical RNA samples											x		x	x
12-Lead ECG												x	x	x
Plasma PK sample [d]				x (Site visit)		x		x		x (Site visit)		x	x	x
Plasma ADA sample						x				x		x	x	x
Serum chemistry [e] and hematology [f]						x		x			x	x	x	x
Plasma biomarker sample						x					x		x	x
Complete physical examination (includes neurologic systems) [g]											x		x	x
Limited physical examination [h]	B					B		B						x

Appendix 1: Schedule of Activities

Assessment/Procedure	Treatment Period										Final Safety and Efficacy Assess.	Follow-Up Period	Early Term. Visit	UV [a]
	OLE (week)													
Study schedule	36	38	40	41	42–50 [b]	52 [c]	54–74 [b]	76 [c]	78–102 [b]	103	104 [c]	116		
Dose number in the WN42171 study	19	20	21		22–26	28	29–39	40	42–53					
Dose level in milligrams (mg)	510 Q2W													
MRI scan [i]	B				B W48 [j]			B			x [j]		x	x
CSF and matching serum samples [k]						x					x		x	
CDR						P&CG		P&CG			P&CG		P&CG	P&CG
ADAS-Cog13						P		P			P		P	P
Verbal Fluency Task						P		P			P		P	P
Coding						P		P			P		P	P
ADCS-ADL						CG		CG			CG		CG	CG
FAQ						CG		CG			CG		CG	CG
MMSE						P		P			P		P	P
EQ-5D						CG		CG			CG		CG	CG
QoL-AD						P&CG		P&CG			P&CG		P&CG	P&CG
ZCI-AD						CG		CG			CG		CG	CG

Appendix 1: Schedule of Activities

Assessment/Procedure	Treatment Period										Final Safety and Efficacy Assess.	Follow-Up Period	Early Term. Visit	UV [a]
	OLE (week)													
Study schedule	36	38	40	41	42–50 [b]	52 [c]	54–74 [b]	76 [c]	78–102 [b]	103	104 [c]	116		
Dose number in the WN42171 study	19	20	21		22–26	28	29–39	40	42–53					
Dose level in milligrams (mg)	510 Q2W													
RUD-Lite						CG		CG			CG		CG	CG
NPI-Q						CG		CG			CG		CG	CG
C-SSRS SLV						P		P			P		P	P
Vital signs [l]	B	B	B	B	B	B	B	B	B		x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [m]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [n]	B	B	B		B	B	B	B	B					
Study drug administration [o]	x	x	x		x	x	x	x	x					

Appendix 1: Schedule of Activities

Aβ=amyloid beta; ADA=anti-drug antibody; ADAS-Cog13 = Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer's Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormality–edema/effusion; ARIA-H = amyloid-related imaging abnormality–microhemorrhage/hemosiderin deposition; Assess.= assessment; CDR = Clinical Dementia Rating; CSF = cerebrospinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-5 Dimension Questionnaire; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory Questionnaire; OLE = open-label extension; PK = pharmacokinetic; Q2W = every 2 weeks; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; T4 = thyroxine; Term. = termination; UV = unscheduled visit; ZCI-AD = Zarit Caregiver Interview for Alzheimer's Disease.

B = before study drug administration; P = participant completion; P&CG = participant and caregiver completion; CG = caregiver completion

Notes: The visit window is ± 3 days. It is recommended that not more than 2 doses are given (i.e., 2 × 510 mg Q2W) within 28 days. Participants should return to initial planned schedule for subsequent visits.

[a] The relevant assessments will be determined by the Principal Investigator per clinical judgment, not necessary to include all assessments listed above. An additional plasma and RNA blood sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E); following new or worsened ARIA-E.

[b] At applicable sites, administration of gantenerumab may be performed by a mobile nursing professional at the participant's home or another suitable location, such as a nursing center, to improve access and convenience for participants participating in the study.

[c] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vital signs, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per the schedule of activities, they may be performed up to 4 weeks out of window.

[d] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as soon as practicable (e.g., at an unscheduled visit or the next study visit) following a MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria (e.g., during an unscheduled visit).

[e] Serum chemistry includes AST, ALT, ALP, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). Hemoglobin A_{1c}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after a meal.

[f] Hematology includes WBC count, RBC count (with morphology), hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[g] A complete physical examination, performed at specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated.

[h] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[i] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[j] Includes resting-state functional MRI and DTI outcome measures, where available.

[k] Lumbar puncture will be performed only in participants who were randomized in the WN29922 or WN39658 studies based on CSF Aβ and tau level results. It must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing (if applicable).

[l] Vital signs include measurements of pulse rate, respiratory rate, systolic and diastolic blood pressure while the participant is in a seated position, and temperature. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[m] After informed consent has been obtained, all adverse events will be reported until the participant's final visit (including long-term follow-up visits).

[n] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[o] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by SC injection (full details are provided in the pharmacy manual). Participants should be observed for at least 1 hour after dosing. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

Appendix 1: Schedule of Activities

Table 3 Schedule of Activities for Participants Who Have Completed the OLE Part of Parent Study WN29922 or WN39658

Assessment/Procedure	Screening	Treatment Period										Final Safety and Efficacy Assess.	FU	Early Term. Visit	UV [a]
		OLE (week)													
Study schedule	While in parent study to -1 day before first doing visit	36	38	40	41	42–50 [b]	52 [c]	54–74 [b]	76 [c]	78–102 [b]	103	104 [c]	116		
Dose number in the WN42171 study		1	2	3		4–8	9	10–20	21	22–34					
Dose level in milligrams (mg)		510 Q2W													
Informed consent(s)	x														
Review of inclusion and exclusion criteria		x [e]													
Medical history, personal status, and demographics	x														
Weight and height [d]		x [e]					x		x			x	x	x	x
Clinical RNA samples		x [e]										x		x	x
Coagulation (PT)		x [e]													
12-Lead ECG		x [e]											x	x	x
Plasma PK sample [f]		x			x (Site visit)		x				x (Site visit)		x	x	x

Appendix 1: Schedule of Activities

Assessment/Procedure	Screening	Treatment Period										Final Safety and Efficacy Assess.	FU	Early Term. Visit	UV [a]
		OLE (week)													
Study schedule	While in parent study to -1 day before first doing visit	36	38	40	41	42–50 [b]	52 [c]	54–74 [b]	76 [c]	78–102 [b]	103	104 [c]	116		
Plasma ADA sample		x					x				x		x	x	x
Serum chemistry [g] and hematology [h]		x [e]					x		x			x	x	x	x
Plasma biomarker sample		x [e]					x					x		x	x
Complete physical examination (includes neurologic systems)[i]												x		x	x
Limited physical examination [j]		x [e]					B		B						x
MRI scan [k, l]		B [e]				B W48			B			x		x	x
CSF and matching serum samples [m]							x					x		x	
CDR		x [e]					P&CG		P&CG			P&CG		P&CG	P&CG
ADAS-Cog13		x [e]					P		P			P		P	P
Verbal Fluency Task		x [e]					P		P			P		P	P
Coding		x [e]					P		P			P		P	P

Appendix 1: Schedule of Activities

Assessment/Procedure	Screening	Treatment Period										Final Safety and Efficacy Assess.	FU	Early Term. Visit	UV [a]
		OLE (week)													
Study schedule	While in parent study to -1 day before first doing visit	36	38	40	41	42–50 [b]	52 [c]	54–74 [b]	76 [c]	78–102 [b]	103	104 [c]	116		
ADCS-ADL		x [e]					CG		CG			CG		CG	CG
FAQ		x [e]					CG		CG			CG		CG	CG
MMSE		x [e]					P		P			P		P	P
EQ-5D		x [e]					CG		CG			CG		CG	CG
QoL-AD		x [e]					P&CG		P&CG			P&CG		P&CG	P&CG
ZCI-AD		x [e]					CG		CG			CG		CG	CG
RUD-Lite		x [e]					CG		CG			CG		CG	CG
NPI-Q		x [e]					CG		CG			CG		CG	CG
C-SSRS SLV		x [e]					P		P			P		P	P
Vital signs [n]		B	B	B	B	B	B	B	B	B		x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [o]		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [p]		B	B	B		B	B	B	B	B					
Study drug administration [q]		x	x	x		x	x	x	x	x					

Appendix 1: Schedule of Activities

ADAS-Cog13 = Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormality–edema/effusion; ARIA-H = amyloid-related imaging abnormality–microhemorrhage/hemosiderin deposition; assess.= assessment; CDR = Clinical Dementia Rating; CSF = cerebrospinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; FU = follow-up; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory Questionnaire; PK = pharmacokinetic; PT = prothrombin time; Q2W = every 2 weeks; QoL–AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; term.= termination; UV = unscheduled visit; ZCI-AD = Zarit Caregiver Interview for Alzheimer's Disease.

B = before study drug administration; P = participant completion; P&CG = participant and caregiver completion; CG = caregiver completion

Notes: The visit window is ± 3 days and +3 days for OLE non-dosing Day 4. It is recommended that not more than 2 administrations are given (i.e., 2 × 510 mg Q2W) within 28 days. Participants should return to initial planned schedule per randomization for subsequent visits.

For participants for whom the uptitration in the parent study took longer than 34 weeks to complete, the first visit in Study WN42171 will be adapted according to the schedule of the visits they had in the parent study.

[a] The relevant assessments will be determined by the Principal Investigator per clinical judgment, not necessary to include all assessments listed above. An additional plasma and RNA blood sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E); following new or worsened ARIA-E.

[b] At applicable sites, administration of gantenerumab may be performed by a mobile nursing professional at the participant's home or another suitable location, such as a nursing center, to improve access and convenience for participants participating in the study.

[c] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vital signs, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per schedule of activities they may be performed up to 4 weeks out of window.

[d] Height will be assessed only at the first dosing visit in the WN42171 study.

[e] Only for participants who participated in the OLE part of the parent study who are rolling over to this study: Results of standard-of-care tests or examinations (coagulation, ECG, serum chemistry and hematology, complete physical examination) performed in the parent studies within 4 weeks prior to the visit may be used. MRI, C-SSRS, and cognitive scale results may be used if they have been performed within 6 months prior to Day 1. MRI must have been performed after the last dose in the parent study. If a clinical RNA sample or a plasma biomarker sample or a CSF and matching serum sample was collected at visit Week 104 of the parent study, another one does not have to be collected.

[f] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as soon as practicable (e.g., at an unscheduled visit or the next study visit) following a MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria (e.g., during an unscheduled visit).

[g] Serum chemistry includes AST, ALT, ALP, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). Hemoglobin A_{1c}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after a meal.

[h] Hematology includes WBC count, RBC count (with morphology), hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[i] A complete physical examination, performed at specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated.

[j] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[k] MRI must be performed at least 7 days before dosing, and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[l] Includes resting-state functional MRI and DTI outcome measures, where available.

[m] Lumbar puncture will be performed only in participants who were randomized in the WN29922 or WN39658 studies based on CSF Aβ and tau level results. It must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing (if applicable).

[n] Vital signs include measurements of pulse rate, respiratory rate, systolic and diastolic blood pressure while the participant is in a seated position, and temperature. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[o] After informed consent has been obtained, all adverse events will be reported until the participant's final visit (including long-term follow-up visits).

[p] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[q] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by SC injection (full details are provided in the pharmacy manual). Participants should be observed for at least 1 hour after dosing. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

Appendix 2 Management Rules for Amyloid-Related Imaging Abnormalities

Event	Characteristic	Action to Be Taken
ARIA-E	Asymptomatic and mild (Bioclinica severity 1)	• Continue study drug according to the schedule of administration (including uptitration). • Perform MRI scans at 4-week intervals until ARIA-E resolves. • Then, resume the standard MRI schedule.
	Asymptomatic and mild+ (Bioclinica severity 2) or moderate (Bioclinica severity 3)	**During uptitration period:** • Continue study drug at the same dose level and do not uptitrate. • Perform MRI scans at 4-week intervals until ARIA-E resolves. • Once ARIA-E resolves, continue uptitration and resume the standard MRI schedule. **During treatment period (at target dose):** • Continue study drug according to the schedule of administration. • Perform MRI scans at 4-week intervals until ARIA-E resolves. • Then, resume the standard MRI schedule.
	Asymptomatic and moderate+ (Bioclinica severity 4) or severe (Bioclinica severity 5) Or Symptomatic ARIA-E [a] of any severity (Bioclinica severity 1–5)	**During uptitration period:** • Temporarily interrupt study drug. • Perform MRI scans at 4-week intervals until ARIA-E (and any ARIA-E symptom/s) resolves. • Once ARIA-E (and any ARIA-E symptom/s) resolves, reintroduce study drug at the dose level given at the time the event was detected. • Perform an MRI scan after two consecutive doses. • If no new ARIA-E is detected, continue uptitration and resume the standard MRI schedule. **During treatment period (at target dose):** • Temporarily interrupt study drug. • Perform MRI scans at 4-week intervals until ARIA-E (and any ARIA-E symptom/s) resolves. • Once ARIA-E (and any ARIA-E symptom/s) resolves, reintroduce study drug. • Perform an MRI scan after two consecutive doses. • If no new ARIA-E is detected, resume the standard MRI schedule.
	Any recurrence of ARIA-E	• Treat as above.
ARIA-H	Without disseminated LH	• Continue study drug according to the schedule of administration (including uptitration). • Perform MRI scans according to the standard MRI schedule.
	Disseminated LH	• Permanently discontinue study drug.

Appendix 2: Management Rules for Amyloid-Related Imaging Abnormalities

ARIA-E = amyloid-related imaging abnormality–edema/effusion; ARIA-H = amyloid-related imaging abnormality–microhemorrhage/hemosiderin deposition; LH = leptomeningeal hemosiderosis; MRI = magnetic resonance imaging; PK=pharmacokinetic; Q4W=every 4 weeks.

Notes:

- Disseminated LH is defined as more than three focal leptomeningeal hemosiderosis.
- If ARIA-E and disseminated LH co-occur, the more conservative management rule will apply.
- The investigator may choose to perform additional MRI monitoring for ARIA at any time.
- In exceptional cases of 1) an ARIA-E that is asymptomatic with Bioclinica severity 1 and considered stable over consecutive MRI images by the Sponsor and investigator; or 2) symptomatic ARIA-E for which the imaging evidence of ARIA-E has resolved but the CNS symptoms continue, gantenerumab can be either reintroduced or uptitrated, as applicable, and Q4W MRI monitoring may no longer be necessary, as determined by the Sponsor and investigator.
- A PK sample will be obtained as soon as soon as practicable (e.g., at an unscheduled visit or the next study visit) following a MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria (e.g., during an unscheduled visit).
- An additional plasma and RNA sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E).

[a] Symptomatic ARIA-E is defined as onset or worsening of CNS symptom(s) that is/are attributable to ARIA-E MRI findings in the judgement of the Principal Investigator.

PROTOCOL

TITLE:	**AN OPEN-LABEL, MULTICENTER, ROLLOVER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF LONG-TERM GANTENERUMAB ADMINISTRATION IN PARTICIPANTS WITH ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN42171
VERSION NUMBER:	4
EUDRACT NUMBER:	2020-000766-42
IND NUMBER:	102,266
NCT NUMBER:	NCT04374253
TEST PRODUCT:	Gantenerumab (RO4909832)
MEDICAL MONITOR:	[redacted], MBBS, Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic signature and stamp on the final page of this document.

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocols		
Version	**Date Final**	**Country**	**Version**	**Date Final**
4	See electronic date stamp on the final page of this document.	—	—	—
3 [a]	10 May 2022	—	—	—
2	7 December 2021	China	2	17 December 2021
1	7 March 2020	Taiwan	Addendum 1	15 November 2021
		United Kingdom	Addendum 1	7 April 2021
		France	Addendum 2	7 April 2021
		France	Addendum 1	18 February 2021

[a] Version 3 was demoted incorrectly in anticipation of refinalization, but the final decision is to issue new version to avoid confusion.

PROTOCOL AMENDMENT, VERSION 4:
RATIONALE

Protocol WN42171 has been amended primarily to extend the open-label treatment (OLE) period from 2 to 4 years. The changes to the protocol, along with a rationale for each change, are summarized below. Note that as Version 3 of the protocol was either withdrawn or not submitted, Version 4 will reflect all changes from Version 2 in italics.

- Section 1.3.1 has been updated to reflect that with the 2-year extension participants will receive open-label gantenerumab for up to 4 years.
- Sections 1.2.1 and 1.3.2.3 have been updated to reflect that Studies WN25203 and WN28745 are completed.
- Section 1.3.2.3 has been updated to clarify that no interactions between positron emission tomography (PET) tracers and the coronavirus disease 2019 (COVID-19) vaccines are expected to occur based on the available information.
- The secondary efficacy objective included change over time in cognition and/or function. The reference to “change over time of other outcomes” has been removed since the other outcomes are exploratory efficacy endpoints.
- Section 3.1.1 has been updated to include that the participants will be treated for 4 years with the last visit in the study at OLE-Week 208 and the follow-up visit at OLE-Week 220. The study period extension will allow the collection of more information on the long-term safety and tolerability of gantenerumab in Alzheimer’s Disease (AD) and its efficacy in the context of long-term exposure, thus increasing understanding of gantenerumab’s long term safety and efficacy profile. In addition, it will allow to better understand the long-term effect of gantenerumab on the pathophysiology of AD as well as changes on Study biomarkers.
- Section 3.2 has been updated to reflect that with the 2-year extension, the total duration of the study from baseline visit is expected to be approximately 4 years with the end of the study expected to occur by the end of 2026.
- Section 3.3.3.2 has been added to include the rationale for the additional 2 years. The extension of the study treatment duration from 2 to 4 years will allow the collection of more longitudinal safety and efficacy information of gantenerumab in AD.
- Sections 4.4.1 and 4.4.2 have been updated to reflect less stringent requirements regarding permitted medication that do not have an impact on participant safety and to clarify that study drug should be temporarily interrupted whilst anticoagulation therapy is ongoing.
- Section 4.4.1 has been updated to clarify that the administration of COVID-19 vaccines will be considered, just as with other vaccinations, as a concomitant medication and that it is recommended to avoid vaccination in the 48 hours around the study dug injection to facilitate the correct attribution of adverse events (AEs).

- Section 4.5.3 has been amended to clarify that collecting ethnicity data facilitates evaluation of whether gantenerumab is metabolized or eliminated differently or if the treatment effect will be different in participants of different ethnic origins.
- Sections 4.5.4, 4.5.6.1, 4.5.7.3, 4.5.12, 4.5.13, 4.6.1 and Appendix 1 have been amended to reflect that OLE-W104 is a dosing visit and not the final efficacy and safety visit, to include additional visits during the study extension with the last visit in the study at OLE-Week 208 and to reflect that the follow-up visit will be at OLE-Week 220 and not at OLE-W116.
- Section 4.5.6.13 has been updated to reflect that the Zarit Caregiver Interview for Alzheimer's Disease (ZCI-AD) scale is also captured electronically. This was omitted in error.
- Section 5.3.5.4 has been amended to clarify reporting of serious or severe secondary events.
- The reporting of adverse events and serious adverse events related to preexisting conditions prior to the parent study baseline has been clarified to ensure the correct collection of data in view of the combined analysis with the data from the parent studies (Sections 5.3.5.12 and 5.3.5.13).
- The Medical Monitor and applicable contact information have been aligned throughout the protocol and deleted from Section 5.4.1. To avoid the inclusion of outdated phone numbers in the protocol, the protocol refers to the Emergency Medical Call Center Help Desk, which will always have an up-to-date list of Medical Monitor and Medical Responsible contact information.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in *italics*. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**AN OPEN-LABEL, MULTICENTER, ROLLOVER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF LONG-TERM GANTENERUMAB ADMINISTRATION IN PARTICIPANTS WITH ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN42171
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TEST PRODUCT:	Gantenerumab (RO4909832)
MEDICAL MONITOR:	[redacted], MBBS, Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____
Principal Investigator's Name (print)

_____ _____
Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**AN OPEN-LABEL, MULTICENTER, ROLLOVER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF LONG-TERM GANTENERUMAB ADMINISTRATION IN PARTICIPANTS WITH ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN42171
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EUDRACT NUMBER:	2020-000766-42
IND NUMBER:	102,266
NCT NUMBER:	NCT04374253
TEST PRODUCT:	Gantenerumab (RO4909832)
PHASE:	Phase IIIb
INDICATION:	Alzheimer's disease
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the safety, tolerability, and efficacy of long-term administration of open–label gantenerumab in participants with Alzheimer's disease (AD) who completed Study WN29922 or WN39658. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Objective: Safety	Corresponding Endpoint
● To evaluate the safety and tolerability of long-term gantenerumab administered by SC injection	● Nature, frequency, severity, timing, and outcomes of adverse events and serious adverse events ● Physical examinations (including neurologic systems), vital signs, ECG, laboratory tests, and C-SSRS ● Nature, frequency, severity, and timing of ARIA-E and ARIA-H ● Nature, frequency, severity, timing, and outcomes of injection-site reactions ● Incidence of treatment discontinuations for adverse events ● Incidence of adverse events of special interest

Secondary Objective: Efficacy	Corresponding Endpoints
● To evaluate the efficacy of long-term gantenerumab administered by SC injection	● The change over time in cognition *and/or* function as measured by the following: – CDR – MMSE – ADAS-Cog11 and ADAS-Cog13 – Verbal Fluency Task – Coding – FAQ – ADCS-ADL
Exploratory Objective: Efficacy	Corresponding Endpoints
● To evaluate the efficacy of long-term gantenerumab administered by SC injection	● The change over time in: – Health-related quality of life, as assessed by the QoL-AD scale – Behavioral and neuropsychiatric symptoms of AD, as measured by the NPI-Q – Caregiver burden, as assessed by the ZCI-AD scale – Elements of resource utilization, as assessed by the RUD-Lite
Exploratory Pharmacokinetic Objective	Corresponding Endpoint
● To characterize the PK profile of gantenerumab administered by SC injection	● Plasma concentration of gantenerumab administered subcutaneously at specified timepoints
Immunogenicity Objective	Corresponding Endpoint
● To evaluate the immune response to gantenerumab administered by SC injection	● Prevalence of ADAs at baseline and incidence of ADAs during the study
Exploratory Biomarker Objective	Corresponding Endpoints
● To evaluate the long-term effects of gantenerumab administered by SC injection	● Brain amyloid load over time, as measured by amyloid PET scan in a subset of participants ● Brain tau load over time, as measured by tau PET scan in a subset of participants ● CSF markers of disease over time in a subset of participants, including, but not limited to, $A\beta_{1-42}$, t–tau, and p-tau ● MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures; changes in functional brain connectivity; or changes in the integrity of white matter, in all participants. ● Blood and plasma markers over time

Exploratory Health Status Utility Objective	Corresponding Endpoint
• To evaluate the health status utility scores of participants treated with gantenerumab	• Health outcome in participant and caregiver, as measured by EQ-5D

AD=Alzheimer's disease; ADAS-Cog11=Alzheimer's Disease Assessment Scale-Cognition Subscale 11; ADAS-Cog13= Alzheimer's Disease Assessment Scale-Cognition Subscale 13; ADCS-ADL=Alzheimer's Disease Cooperative Study Group-Activities of Daily Living; ARIA-E=amyloid-related imaging abnormality-edema/effusion; ARIA-H=amyloid-related imaging abnormality-microhemorrhage/hemosiderin deposition; CDR=Clinical Dementia Rate; CSF=Cerebrospinal fluid; C-SSRS=Columbia-Suicide Severity Rating Scale; EQ-5D=EuroQoL 5–Dimension Questionnaire; FAQ=Functional Activities Questionnaire; MRI=magnetic resonance imaging; NPI-Q=Neuropsychiatric Inventory Questionnaire; PET=positron emission tomography; PK=pharmacokinetic; p–tau=phosphorylated-tau; SC=subcutaneous; RUD-Lite=Resource Utilization in Dementia–Lite; t-tau=total tau; ZCI-AD=Zarit Caregiver Interview for Alzheimer's Disease.

Study Design

Description of Study

This is an open-label, multicenter, rollover study to evaluate the safety, tolerability, and efficacy of long-term administration of open-label gantenerumab in participants with AD who completed study WN29922 or WN39658, either the double-blind or open-label extension (OLE) part, as applicable (parent study). The blind to the study treatment allocation during the parent study will be maintained to protect study integrity.

Participants who have completed study WN29922 or WN39658, either the double-blind or OLE part as applicable, will be eligible to participate in this study. Participants who discontinued early from study treatment during Study WN29922 or WN39658, regardless of the reason, will not be eligible for this study.

Informed consent should be obtained from participants while they are in the parent study (WN29922 or WN39658) including in the safety follow-up, until a day before the first dose in the study WN42171. In special situations, informed consent can be obtained at a later timepoint upon providing an appropriate rationale to the Sponsor, and it must be obtained before any study procedures in this study are performed.

The first administration of gantenerumab in this study will be as follows:

- For participants who completed the double-blind part and did not enter the OLE part of study WN29922 or WN39658: The first administration of open-label gantenerumab should take place approximately 2 weeks after the last efficacy and safety visit of the double-blind part of the parent study (WN29922 or WN39658) and will be considered the OLE baseline visit (OLE Day 1).
- For participants who completed the double-blind part and the OLE part of study WN29922 or WN39658, the first administration of gantenerumab in this study should take place approximately 2 weeks after the OLE Week 34 visit or the final dose visit in the study WN29922 or WN39658 OLE. Participants who have a gap in their transition between the OLE part of the parent study (WN29922 or WN39658) and this study, for unforeseen reasons, will roll over to this study continuing the schedule of activities as per their last visit in the OLE part of the parent study (WN29922 or WN39658. Discussion with the Sponsor is recommended.

Participants with evidence of amyloid-related imaging abnormality–edema/effusion (ARIA-E) on the last per-protocol study magnetic resonance imaging (MRI) scan report in Study WN29922 or WN39658, either its double-blind or OLE part, as applicable, will be retained in the WN29922 or WN39658 study until the ARIA-E finding is resolved. They may then enroll in Study WN42171.

For those enrolling from the OLE part, the first visit of the participants in study WN42171 will be adapted according to the schedule of the visits of each participant in the parent study.

The data from the last visit in the studies WN29922 or WN39658 (e.g., final efficacy and safety visit of the double-blind part, or last visit in the WN29922 or WN39658 OLE part) will be used as the data for the first visit in this study if the two visits take place within 4 weeks of each other. All cognitive scales, and the C-SSRS do not need to be repeated if they were performed within 6 months in the previous parent study. The MRI scan does not need to be repeated if performed within 6 months in the previous parent study (WN29922 or WN39658) and following the final study drug dose in the parent study. Vital signs and urine pregnancy test will have to be performed at the first visit in this study before dosing. MRI and urine pregnancy test results must be available before dosing.

In this study, participants who were in the active double-blind arm in the parent study (WN29922 or WN39658) will continue receiving open-label gantenerumab 510 mg SC Q2W, and those participants who were in the placebo double-blind arm will go through a full uptitration scheme while retaining the blinding to the previous treatment allocation. If there is a delay in a participant's transition between the OLE part of the parent study (WN29922 or WN39658) and this study (for instance, due to delays in the approval of this study at a site) that goes beyond a reasonable time frame as determined by the Sponsor, the participant may be asked to start at the dose they were at previously when they completed the parent study and to perform a safety MRI before receiving the target dose. In this case, such decisions will be made after discussion with the Sponsor.

The dosing schedule and the schedule of activities will be different for participants, depending on whether they completed the OLE part of the study WN29922 or WN39658, which covers the uptitration phase for the participants in the placebo arm, or if they completed only the double–blind part.

Following baseline assessments (i.e., OLE Day 1 either in this protocol or in the parent protocol), each participant will be treated for *4* years. *The study duration has been extended from 2 to 4 years in order to collect more information on the long-term safety and tolerability of gantenerumab in AD and its efficacy in the context of long-term exposure and to increase the overall number of participant-years of exposure, thus increasing understanding of gantenerumab's long-term safety and efficacy profiles. Unless participants are eligible and choose to enroll in an alternative gantenerumab OLE study that becomes available,* the final dose of study drug will be administered at OLE Week *206*. At the end of the treatment period, all participants will undergo an OLE Week *208* visit. Participants will be asked to come back for a follow-up visit at OLE Week *220 unless they are transitioning to an alternative gantenerumab OLE study that becomes available*.

Participants who discontinue study drug at any time during this study will be asked to complete an early termination visit 2 weeks after their final dose and also return for collection of safety data (except safety MRI) and limited efficacy data (i.e., secondary endpoints).

Participants who do not meet the criteria for participation in this study (screening failure) may be re-screened. The investigator will record reasons for screening failure in the screening log.

Substudies

The substudies associated with study WN42171 will be described in separate protocols, and participants consenting to enroll in these substudies will be asked to sign the associated Informed Consent Forms. To date, two optional substudies are associated with Study WN42171: a longitudinal amyloid positron emission tomography (PET) substudy and a longitudinal tau PET substudy.

The amyloid and tau PET assessments will enable a longitudinal evaluation of the effect of gantenerumab on brain amyloid deposition as measured by florbetaben or flutemetamol PET radioligands and tau burden as measured by [18F]GTP1 (Genentech Tau Probe 1; an investigational radioligand for in vivo imaging of tau protein aggregates) in participants with AD.

The collected PET data are expected to help in understanding the effects of gantenerumab on amyloid and tau pathology over time as well as the relationship between changes in florbetaben/flutemetamol/[18F]GTP1-PET and changes in other endpoints in study WN42171.

Two optional substudies associated with this protocol may be introduced.

In one of them, post-mortem brain tissue may be obtained from participants for evaluation of the effect of long-term gantenerumab therapy on the brain. The opportunity to donate post-mortem brain tissue may be discussed with participants.

In the other one, digital tools that assess the disease progression of the participants may be tested for validation and for other exploratory purposes.

Interested participants would be provided with additional details. Any further procedures, with respect to the optional substudies, will be governed by a separate consent form and separate substudy protocol document.

Independent Data Monitoring Committee

The independent Data Monitoring Committee (iDMC) will evaluate participant safety on a regular basis. In addition to the data defined in the iDMC Charter (e.g., the incidence and nature of adverse events, serious adverse events, adverse events of special interest, ARIA-E, amyloid-related imaging abnormality– microhemorrhage/hemosiderin deposition (ARIA-H), and injection site reactions [ISRs]), the iDMC will review all necessary cumulative data, including efficacy data if necessary, at regular intervals during the study. It is anticipated that these assessments will occur approximately every 3 months *or as detailed in the iDMC charter*. At the time of each review, the iDMC will make appropriate recommendations (e.g., the study should continue as planned, the safety risk management should be modified, the protocol should otherwise be amended, and enrollment should be held pending further safety evaluations).

Decisions will be made after considering the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details, such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities are detailed in the iDMC Charter.

Final decisions will rest with the Sponsor.

In the event, the iDMC which reviews safety in both the parent studies (WN29922 and WN39658), and study WN42171 is no longer required (for instance after the unblinding of the parent studies) evaluation of participant safety *may* be taken over by the Sponsor's Internal Monitoring Committee (IMC), with details documented in an IMC charter.

Number of Participants

The planned enrollment is expected to be no more than approximately 2032 participants with AD but will be determined by the number of participants who complete the parent studies WN29922 and WN39658 and enroll in this study.

Target Population

Inclusion Criteria

Participants must meet the following criteria for study entry:

- Signed Informed Consent Form by the participant with AD and/or the legal authorized representative as per local requirements
- Completed study WN29922 or WN39658, either its double-blind part (participants have reached the 510 mg every 2 weeks [Q2W] dose schedule by the time of completion) or OLE part (participants have received at least 3 doses of 510 mg every 4 weeks [Q4W]), and did not discontinue study drug early
- Ability to comply with the study protocol
- Willingness and ability to complete all aspects of the study (including MRI)
- The participant should be capable of completing assessments either alone or with the help of the caregiver.
- Availability of a person (referred to as the "caregiver" throughout the protocol) who:
  - In the investigator's judgement, has frequent and sufficient contact (e.g., 5 times per week or approximately 10 hours per week) with the participant;
  - In the investigator's judgement, is able to provide accurate information regarding the participant's cognitive and functional abilities, including knowledge about domestic activities, hobbies, routines, social skills, and basic activities of daily life; work and educational history; cognitive performance including memory abilities, language

abilities, temporal and spatial orientation, judgement, and problem solving; emotional and psychological state; and can report any changes in the general health status.

- Agrees to provide information and to complete all aspects of the study at clinic visits (which require partner input for scale completion)
- Signs the necessary Informed Consent Form(s), and has sufficient cognitive capacity to accurately report on the participant's behavior as well as cognitive and functional abilities
- Is fluent in the language used at the site and has sufficiently good general health to have a high likelihood of maintaining the same level of interaction with the participant and participation in study procedures throughout the duration of the study

  Every effort should be made to have same caregiver participate throughout the duration of the study.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception as defined below:
  - Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for at least 16 weeks after the final dose of gantenerumab.
  - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.
  - Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- Agreement not to donate blood or blood products for transfusion for the duration of the study and for 1 year after final dose of study drug.

Exclusion Criteria

Participants who meet any of the following criteria will be excluded from study entry:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within at least 16 weeks after the final dose of study drug

  Women of childbearing potential must have a negative urine pregnancy test at the final visit of the parent study.
- Prematurely discontinued from study WN29922 or WN39658, either its double-blind or OLE part, as applicable, or from study drug, for any reason
- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Received any investigational treatment other than gantenerumab during or since completion of study WN29922 or WN39658, either its double-blind or OLE part, as applicable
- Evidence of disseminated leptomeningeal hemosiderosis (i.e., more than three focal leptomeningeal hemosiderosis)
- Evidence of intracerebral macrohemorrhage
- Use of prohibited medication

- Evidence of ARIA-E on the last MRI scan report in Study WN29922 or WN39658, either its double-blind or OLE part, as applicable

Participants should remain in the parent study, as governed by that protocol, and may enroll in this study once the ARIA-E is resolved.

End of Study

The end of this study is defined as the date when the last participant, last visit, occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last participant, whichever occurs later. The end of the study is expected to occur by the end of *2026*.

In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of this study from baseline visit (OLE Day 1 in either the Study WN42171 protocol or in the parent protocol) to the end of the study (including the follow-up visit) is expected to be approximately *4* years and 3 months. Following uptitration, participants will receive up to *86* doses of gantenerumab 510 mg Q2W. Participants who did not participate in the OLE part of the parent study (WN29922 or WN39658) will also go through an uptitration scheme in the WN42171 study with a duration of at least 34 weeks.

Investigational Medicinal Products

The investigational medicinal product for this study is gantenerumab.

Test Product (Investigational Drug)

Gantenerumab or placebo will be administered by SC injection to all patients.

Statistical Methods

Primary Analysis

The safety analysis population will include all enrolled participants who received at least one dose of study drug in this protocol.

The following safety outcome measures will be summarized using descriptive statistics:

- Nature, frequency, severity, timing, and outcomes of adverse events and serious adverse events
- Physical examinations (including neurological systems), vital signs, ECG, laboratory tests, and Columbia-Suicide Severity Rating Scale (C-SSRS)
- Nature, frequency, severity, and timing of ARIA-E and ARIA-H
- Nature, frequency, severity, timing, and outcomes of injection-site reactions
- Incidence of treatment discontinuations for adverse events
- Incidence of adverse events of special interest

Statistical methods, endpoint definitions, and analyses of the safety endpoints will be described in a Statistical Analysis Plan (SAP).

Determination of Sample Size

The sample size will include all eligible participants who consent to this study. The sample size is expected to be no more than approximately 2032 participants but will be determined by the number of participants who complete the parent studies (WN29922 and WN39658) and enroll in this study.

Interim Analyses

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one or more interim analysis(es), which may include efficacy, safety, and biomarker outcomes. An interim analysis may be considered when the parent pivotal studies WN29922 and WN39658 are completed and the submission folder is under preparation. Details will be pre-specified in a SAP.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
[^{18}F]GTP1	Genentech Tau Probe 1
Aβ	amyloid beta
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADA	anti-drug antibody
ADAS-Cog11	Alzheimer's Disease Assessment Scale–Cognition, Subscale 11
ADAS-Cog13	Alzheimer's Disease Assessment Scale–Cognition, Subscale 13
ADCS-ADL	Alzheimer's Disease Cooperative Study Group–Activities of Daily Living
ADL	activities of daily living
APOE	Apolipoprotein E
APOE ε4-	apolipoprotein E gene allele ε4-
ARIA	amyloid-related imaging abnormality
ARIA-E	amyloid-related imaging abnormality–edema/effusion
ARIA-H	amyloid-related imaging abnormality–microhemorrhage/hemosiderin deposition
BOLD	blood oxygenation level-dependent
CDR	Clinical Dementia Rating
CDR-GS	Clinical Dementia Rating–Global Score
CDR-SOB	Clinical Dementia Rating–Sum of Boxes
COA	clinical outcome assessment
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DTI	diffuse tensor imaging
DSST	Digit Symbol Substitution Test
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EQ-5D	EuroQoL 5-Dimension Questionnaire
E.U.	European Union
FA	fractional anisotropy
FAQ	Functional Activities Questionnaire
FDA	(U.S.) Food and Drug Administration

Abbreviation	Definition
GRE	gradient recalled echo
GTP1	Genentech Tau Probe 1
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ISR	injection-site reaction
IxRS	interactive voice or web-based response system
MAD	multiple ascending dose
MMSE	Mini-Mental State Examination
MN	mobile nursing
MRI	magnetic resonance imaging
MR-NP	Marguerite RoAD (Study WN28745) double-blind placebo (non-pretreated patients in the placebo arm of Study WN28745 during the double-blind phase)
MR-P	Marguerite RoAD (Study WN28745) double-blind active (pretreated patients in the active treatment arm of Study WN28745 during the double-blind phase)
NMDA	N-methyl-D-aspartate
NPI-Q	Neuropsychiatric Inventory Questionnaire
OLE	open-label extension
PD	pharmacodynamics
PET	positron emission tomography
PK	pharmacokinetic
p-tau	phosphorylated tau
Q2W	every 2 weeks
Q4W	every 4 weeks
QoL	quality of life
QoL-AD	Quality of Life–Alzheimer's Disease
RBR	Research Biosample Repository
rs-fMRI	resting-state functional magnetic resonance imaging
RUD-Lite	Resource Utilization in Dementia–Lite
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SR	Scarlet RoAD (Study WN25203)
T4	thyroxine

Abbreviation	Definition
t-tau	total tau
ULN	upper limit of normal
WAIS-IV	Wechsler Adult Intelligence Scale-Fourth Edition
WES	whole exome sequencing
WGS	whole genome sequencing
ZCI-AD	Zarit Caregiver Interview for Alzheimer's Disease

1. BACKGROUND

1.1 BACKGROUND ON ALZHEIMER'S DISEASE

The World Health Organization estimates that around 50 million people worldwide are diagnosed with dementia and that there are 10 million new cases every year. The total number of people with dementia is estimated to reach 82 million in 2030 and will more than triple to 152 million by 2050. Alzheimer's disease (AD) is the most common form of dementia, accounting for 60%–70% of cases (World Health Organization 2019). The prevalence of AD increases with age, with a global prevalence of 5%–8% in people 60 years and older. Because of its increasing prevalence, long duration, and high cost of care, AD is expected to continue to represent a major public health problem for decades to come.

The median survival time following a diagnosis of AD strongly depends on the patient's age at diagnosis and ranges from 8.3 years for persons diagnosed with AD at 65 years old to 3.4 years for those 90 years old (Brookmeyer et al. 2002; Zanetti et al 2009), but some individuals survive as long as 20 years.

It is well recognized that in comparison to other therapeutic domains, there is a real unmet medical need in AD therapy (Gauthier et al. 2016). To date, only five medications have received marketing approval in the European Union and United States to treat the symptoms of AD, including acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists. These approved drugs are recognized to temporarily improve some clinical symptoms of AD in some patients but do not modify progression of the disease (Cummings et al. 2018).

Currently, one compelling therapeutic target (Graham et al. 2017) is amyloid beta (Aβ), and Aβ-targeting therapies remain the major trend in AD drug development (Bachurin et al. 2017). These therapies are based on the amyloid hypothesis that posits Aβ accumulation as the primary factor driving AD pathogenesis (Selkoe 1991; Hardy and Selkoe 2002; Selkoe and Hardy 2016). This Aβ accumulation in the brain begins well before the development of clinical dementia in AD and causes a series of downstream events leading to synaptic dysfunction, inflammation, neurodegeneration, and clinical symptoms. For these reasons, treatments that prevent, slow, or decrease the accumulation of brain Aβ are being tested as therapeutic agents in AD.

1.2 BACKGROUND ON GANTENERUMAB

Gantenerumab (RO4909832) is a recombinant, human monoclonal antibody of the IgG1 subclass directed against the Aβ peptide. Gantenerumab recognizes a conformational epitope of Aβ and has demonstrated activity for both major types of Aβ (Aβ1–40, Aβ1–42). In vitro, gantenerumab recognizes synthetic aggregated Aβ fibrils and Aβ oligomers with high nanomolar affinity (K_D, ~0.6–1.2 nM). The mechanism of action of gantenerumab is primarily clearance of Aβ plaques by antibody-dependent cell-mediated

phagocytosis. Gantenerumab also works via dissociation of Aβ peptide aggregates by direct resolution and by blockade of toxic Aβ oligomers.

Gantenerumab is manufactured by cell culture of a recombinant Chinese hamster ovary K1 mammalian cell line and subsequent purification of the antibody. Gantenerumab drug substance manufacturing was optimized during development to improve process robustness and increase overall process yield, leading to several generations of manufacturing process (G1, G2, G3, and G4). Drug material manufactured by the G4 process is used in pivotal Phase III clinical trials (Studies WN29922 and WN39658). G4 drug material will be used in this study.

1.2.1 Nonclinical and Clinical Studies

Nonclinical evidence has suggested that monoclonal anti-Aβ antibodies may be able to remove and reduce deposition of Aβ aggregates from the brain. In transgenic animal models of AD, vaccination with Aβ or passive immunization with anti-Aβ antibodies resulted in decreased amyloidosis and in improvement of memory function in some transgenic models of cognitive function (Janus et al. 2000). Accumulating clinical evidence also supports that monoclonal Aβ antibodies can bind Aβ and promote its clearance (Salloway et al. 2009; Ostrowitzki et al. 2012; Klein et al. 2019b), reduce deposition of Aβ aggregates, and reduce markers of neurodegeneration in the cerebrospinal fluid (CSF;Roche Research Report No. 1066251). In a Phase I study with the anti-Aβ monoclonal antibody aducanumab, reduction of deposited amyloid as shown on brain amyloid positron emission tomography (PET) imaging was associated with a time- and dose-related slowing of cognitive decline (Sevigny et al. 2016). Because the pathological changes associated with AD develop decades before clinical symptoms emerge, it is thought that earlier intervention may be more effective in arresting or delaying disease progression (Sevigny et al. 2016). Consequently, therapies targeting this process have the potential to significantly alter the progression of the disease. Gantenerumab, a fully human monoclonal antibody targeting aggregated forms of Aβ, such as Aβ oligomers, fibrils, and plaques, is expected to address this need (Bohrmann et al. 2012).

Gantenerumab has been investigated in 10 completed Phase I clinical studies: 3 single ascending dose studies in healthy volunteers and patients with mild to moderate AD (Studies BN18726, JP22474, and BP30042); 2 multiple ascending dose (MAD) studies of patients with mild to moderate AD (Studies NN19866 and JP22431); and 4 bioavailability studies in healthy subjects−1 study comparing the IV and SC formulations of gantenerumab (Study WP22461), 2 studies comparing lyophilized and high-concentration liquid formulations of gantenerumab (Studies WP27951 and BP29113), and 1 study comparing drug substance manufactured through the third and fourth generation (G3 and G4) processes (Study WP40052). A tolerability study that compared injection-site pain between faster and slower SC administration of gantenerumab was also conducted (Study WP39322). Overall, a total of 543 subjects

have participated in the Phase I studies; of these participants, 406 healthy volunteers and 101 patients with mild to moderate AD have received gantenerumab.

Based on results of the MAD Study NN19866 and of the relative bioavailability study (WP27951), the doses of 105 mg SC every 4 weeks (Q4W; equivalent to 60 mg IV Q4W) and 225 mg SC Q4W (equivalent to 130 mg IV Q4W) were initially selected for the Phase III studies WN25203 and WN28745. Following the results of the Study WN25203 futility analysis, these studies were converted into open-label extensions (OLEs) to examine the safety and tolerability of a higher dose of gantenerumab (1200 mg SC Q4W).

Overall, 383 patients enrolled in the OLEs of Studies WN25203 and WN28745. As of 1 May 2019, 363 patients had been exposed to G3 gantenerumab doses higher than 225 mg, and 309 patients reached the target 1200 mg dose. Continuous monitoring of safety data and magnetic resonance imaging (MRI) findings by the Sponsor has not identified any new safety signals in these ongoing studies. Injection-site reactions (ISRs) and amyloid-related imaging abnormalities (ARIAs) remain the only identified risks for gantenerumab. These OLE studies *were completed respectively in 2020 and* in 2021, and patients who *did* not discontinue study treatment at the end of the prescribed study period *were* provided an option to enroll in an open-label rollover study to evaluate the safety and tolerability of long-term administration of gantenerumab (Study WN41874).

Based on safety results from OLE Studies WN25203 and WN28745, and on data from the PET substudies that confirmed the pharmacodynamic (PD) effects of gantenerumab treatment (1200 mg SC Q4W) on Aβ plaque reduction (Klein et al. 2019b), two pivotal multicenter, Phase III studies in patients with early (prodromal to mild) AD were initiated: WN29922 (Graduate 1) and WN39658 (Graduate 2). These studies are examining the efficacy, safety, and tolerability of gantenerumab uptitrated to 510 mg every 2 weeks (Q2W) dosing; they are currently ongoing and are expected to be completed in 2023. Refer to the Gantenerumab Investigator's Brochure for more details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.3.1 Study Rationale

Study WN42171 allows participants previously treated with gantenerumab or placebo for approximately 2 years in the parent Studies WN22992 or WN39658 to continue receiving open-label gantenerumab.

Currently, approved therapies for AD focus on symptomatic approaches that target synaptic function and cognitive enhancement (Cummings 2004). However, the amyloid hypothesis suggests that overproduction of Aβ or failure to effectively clear this peptide contributes to AD (Selkoe and Hardy 2016) and that accumulation of Aβ peptides is a factor contributing to AD progression (Sun et al. 2015). Thus, the targeting of Aβ and

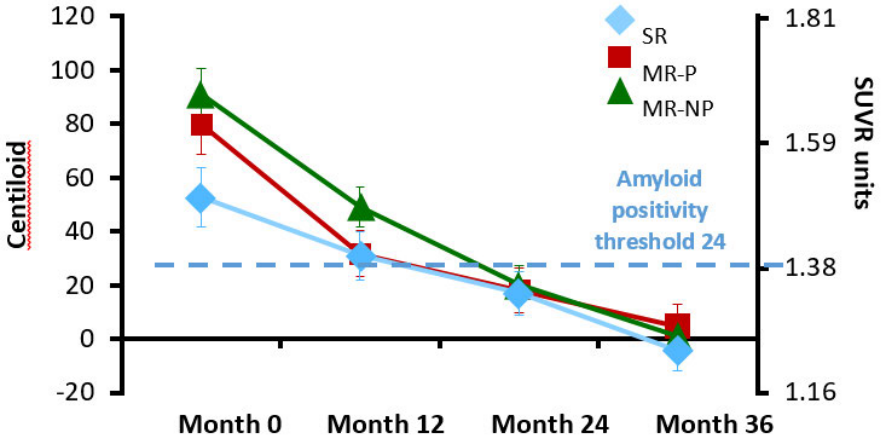
subsequent displacement of Aβ from the brain is a rational approach to modify AD progression.

Accumulating clinical evidence supports that monoclonal Aβ antibodies can bind Aβ and promote its clearance (Salloway et al. 2009; Ostrowitzki et al. 2012; Sevigny et al. 2016; Klein et al. 2019b), reduce deposition of Aβ aggregates, and reduce markers of neurodegeneration in CSF (Ostrowitzki et al. 2017). A Phase I study of aducanumab (Sevigny et al. 2016) and a Phase II study of BAN2401 (Swanson et al. 2018) suggested that reduction of deposited amyloid, as seen on brain amyloid PET imaging, was associated with a dose-related slowing of cognitive decline.

Gantenerumab data from the PET substudies of the WN25203 and WN28745 OLEs confirmed that gantenerumab treatment at a dose of 1200 mg SC Q4W reduced Aβ plaques in patients with AD (Klein et al. 2019b). Overall, 89 patients from the OLEs of Studies WN25203 and WN28745 were included in amyloid PET substudies using florbetapir F18. As of 31 August 2019, of these 89 patients, 67 patients received follow-up scans at Week 52, 42 patients at Week 104, and 30 patients at Week 156 of the OLE.

Results of the PET substudies showed a marked and consistent reduction of amyloid load in patients receiving higher-dose gantenerumab in all three patient groups that were analyzed (Figure 1): 1) MR-NP (non-pretreated patients in the placebo arm of Study WN28745); 2) MR-P (pretreated patients in the active treatment arm of Study WN28745); and 3) SR (patients from Study WN25203). Indeed, amyloid reductions were seen consistently in nearly all patients in the three analyzed subgroups (Figure 2).

Figure 1 Mean (SE) PET Amyloid Reductions in the OLE PET Substudies



Centiloids[a]

SR	52.7 (11.1) n = 20	30.9 (8.9) n = 19	17.0 (8.2) n = 13	**–4.3 (7.5)** n = 10
MR-P	79.6 (10.9) n = 21	31.7 (8.6) n = 21	18.1 (8.3) n = 11	**4.7 (8.0)** n = 8
MR-NP	91.1 (9.6) n = 27	49.1 (7.6) n = 27	20.2 (7.0) n = 18	**0.78 (6.7)** n = 12

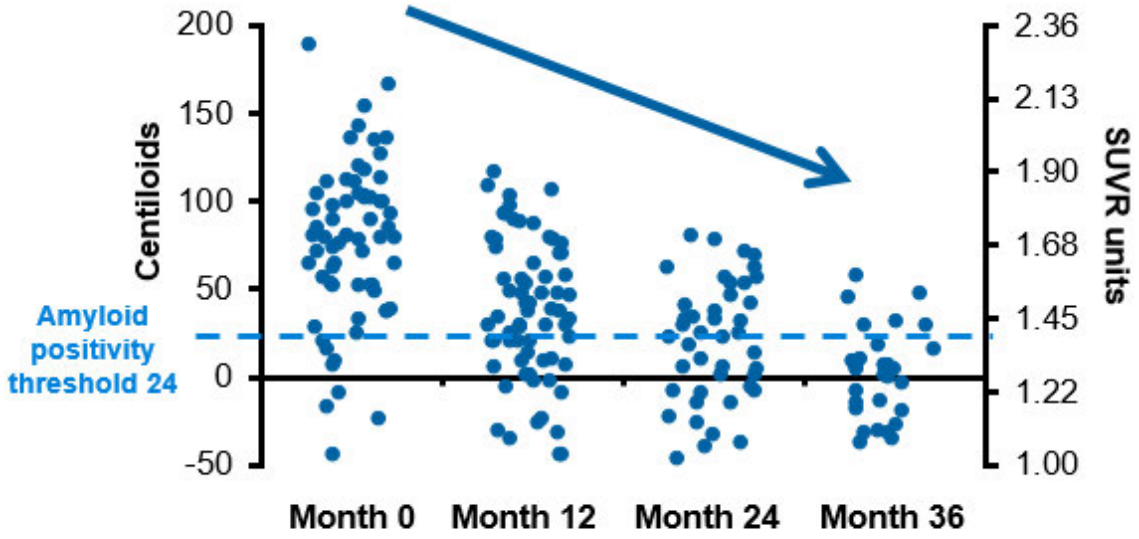
MR-P=Marguerite RoAD (Study WN28745) double-blind active (pretreated patients in the active treatment arm of Study WN28745 during the double-blind phase); MR-NP=Marguerite RoAD (Study WN28745) double-blind placebo (non-pretreated patients in the placebo arm of Study WN28745 during the double-blind phase); OLE = open-label extension; PET = positron emission tomography; SE = standard error; SR = Scarlet RoAD (Study WN25203); SUVR = standardized uptake value ratio.

[a] Analyzed using a mixed-model for repeated measures.

Source: Klein et al. 2019a.

The threshold for amyloid positivity is an important anchor for interpreting the PET substudy results. It is defined as the quantitative threshold that best discriminates pathologically-verified absence of plaques or sparse plaques from moderate to frequent plaques. A centiloid value of 24 is generally recognized as the amyloid positivity threshold (Landau and Jagust 2015; Navitsky et al. 2018; Klein et al. 2019b). Results in the ongoing substudies WN25203 and WN28745 confirm the amyloid plaque removal component of the gantenerumab mechanism of action. The results further show that following 3 years of gantenerumab treatment, 80% of subjects were below the positivity threshold, and 43% of subjects were below a centiloid value of 0, which represents the mean amyloid load of a healthy normal population (Figure 2).

Figure 2 Patient-Level Amyloid Reductions over 3 Years of Treatment in the OLE PET Substudies



Proportion of participants below amyloid positivity threshold

No. of participants	68	67	42	30
% below threshold	**15%**	**37%**	**52%**	**80%**

OLE = open-label extension; PET = positron emission tomography; SUVR = standardized uptake value ratio.
Source: Klein et al. 2019a.

In summary, the PET substudy results demonstrate continued amyloid removal beyond 2 years of gantenerumab treatment. Thus, this study, which provides open-label gantenerumab for 4 additional years to patients already receiving gantenerumab in the parent Study (WN22992 or WN39658), will provide valuable information on how continued amyloid removal may translate into continued clinical effect.

Study WN42171 will also provide the opportunity for participants previously treated with placebo in the double-blind phase of parent Study WN22992 or WN39658 to receive gantenerumab treatment for up to 4 years. To protect study data integrity and to aid the assessment of the long-term effects of gantenerumab, treatment assignment information from the double-blind phase of parent Study WN22992 or WN39658 will remain blinded to the Sponsor, investigator, and participant at least until database lock of the parent studies, which will happen while this study is ongoing.

1.3.2 Safety Overview

Nonclinical characterization of gantenerumab did not show relevant safety findings. No differences between gantenerumab and placebo groups have been observed in laboratory parameters, physical and neurologic examinations, vital signs, or ECG parameters.

The identified risks of gantenerumab treatment are ARIAs and ISRs. Safety data and MRI findings are continuously monitored in all ongoing studies, and no new safety signals have been identified.

The Gantenerumab Investigator's Brochure includes a summary of safety data with gantenerumab SC in participants with AD from Studies WN25203 and WN28745 as well as from Phase I studies with gantenerumab SC and IV.

Providing participants who complete study treatment in the pivotal Studies WN22992 and WN39658 with an opportunity to extend or initiate treatment with open-label gantenerumab in Study WN42171 will allow the collection of more information on the long-term safety and tolerability of gantenerumab in AD. It will also provide more information on its efficacy in the context of long-term exposure. Furthermore, the OLE will increase the overall number of participants exposed to gantenerumab and participant-years of exposure, thus increasing understanding of the safety and efficacy profiles.

1.3.2.1 Amyloid-Related Imaging Abnormalities

ARIAs are one of the most significant adverse events reported in therapies against aggregated forms of Aβ. These findings appear to be dependent on dose-, time-, and apolipoprotein E gene allele ε4- (APOE ε4-) (Piazza and Winblad 2016).

The mechanism underlying the development of amyloid-related imaging abnormality–edema/effusion (ARIA-E) and amyloid-related imaging abnormality–microhemorrhage/hemosiderin deposition (ARIA-H) during anti-amyloid treatment is not yet fully understood. Because antibodies remove Aβ from both the parenchyma and cerebral vasculature, vessels with preexisting amyloid vascular pathology might become transiently more susceptible to leakage of vascular contents. This pathology results in ARIA-E if the leakage consists of proteinaceous fluid and in ARIA-H if the leakage consists of blood products (Sperling et al. 2012). An anti-Aβ therapy that effectively maintains vascular Aβ clearance would allow vascular remodeling and might, over time, decrease the risk of such extravasation events (Sperling et al. 2012). This is consistent with experiences in previous and ongoing studies and with reported data from the long-term extension study of aducanumab treatment (Viglietta et al. 2016).

Understanding of the clinical significance of ARIA by study sponsors, investigators, and regulators has substantially evolved since ARIA events were first seen on MRI scans in

a Phase I clinical trial with bapineuzumab (Black et al. 2010). The accrued clinical evidence with gantenerumab and other N-terminus anti-amyloid antibodies has shown that ARIA events tend to occur early in treatment, are dose- and APOE ε4-dependent, and can be monitored by MRI and managed with dose intervention algorithms.

The Sponsor's experience with managing patients with ARIA findings and increasing understanding of the impact of such findings on patient clinical outcomes has resulted in the introduction of revised ARIA risk mitigation measures in studies with gantenerumab over time. Accordingly, ARIA management has shifted from more cautious management, where an ARIA-E finding resulted in treatment interruption regardless of intensity (Study WN25203 [double-blind]), to less restrictive management, where only moderate-severe intensity ARIA-E and symptomatic ARIA-E findings result in treatment interruption (Studies WN25203 and WN28745: OLE; Studies WN29922 and WN39658). Similarly, the cumulative number of ARIA-H findings that trigger treatment discontinuation was changed from 5 (Studies WN25203 and WN28745 [double-blind]) to 10 (Studies WN25203 and WN28745 [OLE]), to 15 (Studies WN29922 and WN39658). The revised management led to similar and acceptable safety profiles.
In Studies WN29922 and WN39658, safety reviews of unblinded data by an independent Data Monitoring Committee (iDMC) have not identified any new safety signal.

Taking into account the evolving experience with managing ARIA findings, including the finding that continued gantenerumab treatment during episodes of asymptomatic mild ARIA-E was not associated with clinically unfavorable outcomes, the Sponsor intends to examine the safety of continuing gantenerumab treatment through mild to moderate asymptomatic ARIA-E findings and to examine the safety of gantenerumab therapy in the presence of an increased number of ARIA-H microhemorrhages.

Study WN42171 will require an MRI scan documenting the absence of ARIA-E or evidence of disseminated leptomeningeal hemosiderosis prior to the first gantenerumab dose. If ARIA findings occur during the study, MRI monitoring, temporary dose holding, or permanent study drug discontinuation will be implemented according to an ARIA management plan, as described in Appendix 2.

Safety findings, including individual participant and aggregate data, will be reviewed on a regular basis by the Sponsor and by an iDMC. *In the event the iDMC which reviews safety in both the parent Studies (WN29922 and WN39658) and Study WN42171 is no longer required (for instance after the unblinding of the parent studies) evaluation of participant safety may be taken over by the Sponsor's Internal Monitoring Committee (IMC), with details documented in an IMC charter.*

1.3.2.2 Injection-Site Reactions

The incidence of ISRs in gantenerumab-treated patients with up to the target gantenerumab dose (1200 mg SC Q4W) ranged from 36% (Study WN25203 OLE) to 38% (Study WN28745 OLE) as of 1 May 2019. All ISRs were non-serious, mostly mild

to moderate in intensity, and the majority resolved without treatment. The most common signs and symptoms of ISRs included injection-site erythema, redness, swelling, and itching. No patients discontinued study treatment due to ISRs.

1.3.2.3 Overall Benefit–Risk Summary

The benefit–risk assessment of gantenerumab treatment in Study WN42171 is based on the following:

- Gantenerumab has shown evidence of continuous reduction of the amyloid plaque component in up to 3 years of treatment and thus shows potential benefit in slowing the progression of AD.
- Findings from Study WN25203 (Klein et al. 2019), the PRIME study with aducanumab (Sevigny et al. 2016), and from the Phase II study with BAN2401 (Swanson et al. 2018) suggest that reduction in deposited amyloid is associated with a dose-related slowing of cognitive decline, providing additional support for the hypothesis that anti-amyloid treatment may be associated with a beneficial clinical effect.
- Results from the double-blind part of Studies WN25203 and WN28745, as well as from the *completed* OLEs Studies WN25203 and WN28745, showed that ARIA-E findings are mostly asymptomatic, non-serious, of mild severity, and do not require permanent cessation of treatment.
- No new safety signals have been identified from the ongoing Phase III studies with gantenerumab with doses of up to 510 mg Q2W or equivalent, which supports the safety of continued administration of gantenerumab uptitrated to the target dose in the current and planned studies, including Study WN42171.
- Study WN42171 will provide participants with the opportunity to extend treatment with gantenerumab beyond 2 years, thereby providing more information on the long-term safety, tolerability, and efficacy of gantenerumab in AD. Furthermore, the study will increase the overall number of participants exposed to gantenerumab and the patient-years of exposure and increase the understanding of the safety:efficacy profile. Analyzing the long-term safety, tolerability, and efficacy of gantenerumab is of critical importance to help clinicians make informed therapeutic decisions for participants.
- The design of Study WN42171 will allow participants with moderate asymptomatic ARIA-E and with any number of ARIA-H microhemorrhages to continue gantenerumab treatment. This is in line with the evolving understanding of the clinical significance of ARIA by the clinical trial Sponsors and medical community (see Section 3.3.4).
- An iDMC will evaluate safety data on a regular basis, including the incidence and nature of adverse events, serious adverse events, adverse events of special interest, ARIA-E, ARIA-H, and ISRs and will make appropriate recommendations (see Section 3.1.3). *In the event the iDMC which reviews safety in both the parent studies (WN29922 and WN39658) and Study WN42171 is no longer required (for instance after the unblinding of the parent studies), evaluation of participant safety*

may be taken over by the Sponsor's IMC, with details documented in an IMC charter.

- The benefit–risk ratio of conducting Study WN42171 during the Coronavirus Disease 2019 (COVID-19) pandemic remains unchanged. This is supported by the nonclinical and clinical data collected through the development program of gantenerumab where there has been no indication that gantenerumab administration compromised the immune system or made individuals more susceptible to infections. Thus, there are no data or biological rationale suggesting that gantenerumab administration could increase the risk of infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or more severe COVID–19 outcomes.
- Participating in study visits at the investigational sites may however increase the risk of exposure to SARS-COV-2, therefore, whenever appropriate, the Sponsor allows the possibility to perform home visits by adequately trained health care professionals. All necessary precautions will be taken to protect the health of the study participants and minimize the risk of exposure. As such the Principal Investigator, in addition to all appropriate study staff that come into contact with the study participants, will wear personal protective equipment during the visit as per local requirements.
- Based on the available information, no interactions between gantenerumab *or PET tracers* and the COVID-19 vaccines are expected to occur, and no other safety concerns have been identified that would prohibit the vaccination of participants enrolled in the studies where gantenerumab is being investigated for the treatment of AD. Just as with other vaccinations (e.g., influenza), the administration of COVID-19 vaccines will be considered as a concomitant medication in this study.

Overall, the anticipated benefit–risk profile of gantenerumab supports open-label gantenerumab treatment in Study WN42171 for participants who completed either the double-blind or OLE part of parent Study WN29922 or WN39658.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, tolerability, and efficacy of long-term administration of open-label gantenerumab in participants with AD who completed Study WN29922 or WN39658. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 SAFETY OBJECTIVE

2.1.1 Primary Objective: Safety

The primary objective for this study is to evaluate the safety and tolerability of long-term gantenerumab administered by SC injection on the basis of the following endpoints:

- Nature, frequency, severity, timing, and outcomes of adverse events and serious adverse events

- Physical examinations (including neurologic systems), vital signs, ECG, laboratory tests, and Columbia-Suicide Severity Rating Scale (C-SSRS)
- Nature, frequency, severity, and timing of ARIA-E and ARIA-H
- Nature, frequency, severity, timing, and outcomes of ISRs
- Incidence of treatment discontinuations for adverse events
- Incidence of adverse events of special interest

2.2 EFFICACY OBJECTIVE

2.2.1 Secondary Objective: Efficacy

The secondary objective for this study is to evaluate the efficacy of long-term gantenerumab administered by SC injection on the basis of the following endpoints:

- Change over time in cognition *and/or* function as measured by the following:
  - Clinical Dementia Rating (CDR)
  - Mini-Mental State Examination (MMSE)
  - Alzheimer Disease Assessment Scale–Cognition, Subscale 11 (ADAS-Cog11) and Alzheimer Disease Assessment Scale–Cognition, Subscale 13 (ADAS-Cog13)
  - Verbal Fluency Task
  - Coding
  - Functional Activities Questionnaire (FAQ)
  - Alzheimer Disease Cooperative Study Group–Activities of Daily Living (ADCS-ADL)

2.2.2 Exploratory Objective: Efficacy

The exploratory objective for this study is to evaluate the efficacy of long-term gantenerumab administered by SC injection on the basis of the following endpoints:

- Change over time in:
  - Health-related quality of life, as assessed by the Quality of Life–Alzheimer's Disease (QoL-AD) scale
  - Behavioral and neuropsychiatric symptoms of AD, as measured by the Neuropsychiatric Inventory Questionnaire (NPI-Q)
  - Caregiver burden, as assessed by the Zarit Caregiver Interview for Alzheimer's Disease (ZCI-AD) scale
  - Elements of resource utilization, as assessed by the Resource Utilization in Dementia–Lite (RUD-Lite)

2.3 PHARMACOKINETIC OBJECTIVE

The exploratory pharmacokinetic (PK) objective for this study is to characterize the PK profile of gantenerumab administered by SC injection on the basis of the following endpoint:

- Plasma concentration of gantenerumab administered SC at specified timepoints

2.4 IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is to evaluate the immune response to gantenerumab administered by SC injection on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study

2.5 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to evaluate the long-term effects of gantenerumab administered by SC injection based on the following endpoints:

- Brain amyloid load over time, as measured by amyloid PET scan in a subset of participants
- Brain tau load over time, as measured by tau PET scan in a subset of participants
- CSF markers of disease over time in a subset of participants, including, but not limited to, $A\beta_{1-42}$, total tau (t-tau), and phosphorylated tau (p-tau)
- MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures; changes in functional brain connectivity; or changes in the integrity of white matter in all participants
- Blood and plasma markers over time

2.6 HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate the health status utility scores of participants treated with gantenerumab on the basis of the following endpoint:

- Health outcomes in participant and caregiver, as measured by EuroQol 5-Dimension Questionnaire (EQ-5D)

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

Study WN42171 is an open-label, multicenter, rollover study to evaluate the safety, tolerability, and efficacy of long-term administration of open-label gantenerumab in participants with AD who completed Study WN29922 or WN39658, either the double-blind or OLE part, as applicable (parent study). The blind to the study treatment allocation during the parent study will be maintained to protect study integrity.

Participants who have completed Study WN29922 or WN39658, either the double-blind or OLE part as applicable, will be eligible to participate in this study. Participants who discontinued early from study treatment during Study WN29922 or WN39658, regardless of the reason, will not be eligible for this study.

Informed consent should be obtained from participants while they are in the parent study (WN29922 or WN39658) including in the safety follow-up, until a day before the first dose in the Study WN42171. In special situations, informed consent can be obtained at a later timepoint upon providing an appropriate rationale to the Sponsor, and it must be obtained before any study procedures in this study are performed.

The first administration of gantenerumab in this study will be as follows:

- For participants who completed the double-blind part and did not enter the OLE part of Study WN29922 or WN39658: The first administration of open-label gantenerumab should take place approximately 2 weeks after the last efficacy and safety visit of the double-blind part of the parent study (WN29922 or WN39658) and will be considered the OLE baseline visit (OLE Day 1).
- For participants who completed the double-blind part and the OLE part of Study WN29922 or WN39658, the first administration of gantenerumab in this study should take place approximately 2 weeks after the OLE Week 34 visit or the final dose visit in the Study WN29922 or WN39658 OLE. Participants who have a gap in their transition between the OLE part of the parent study (WN29922 or WN39658) and this study, for unforeseen reasons, will roll over to this study continuing the schedule of activities as per their last visit in the OLE part of the parent study (WN29922 or WN39658). Discussion with the Sponsor is recommended.

Participants with evidence of ARIA-E on the last per-protocol study MRI scan report in Study WN29922 or WN39658, either its double-blind or OLE part, as applicable, will be retained in the WN29922 or WN39658 study until the ARIA-E finding is resolved. They may then enroll in Study WN42171. *For those enrolling from the OLE part*, the first visit of the participants in Study WN42171 will be adapted according to the schedule of the visits of each participant in the parent study.

The data from the last visit in study WN29922 or WN39658 (e.g., final efficacy and safety visit of the double-blind part or last visit in the WN29922 or WN39658 OLE part) will be used as the data for the first visit in this study if the two visits take place within 4 weeks of each other. All cognitive scales, and the C-SSRS do not need to be repeated if they were performed within 6 months in the previous parent study. The MRI scan does not need to be repeated if performed within 6 months in the previous parent study (WN29922 or WN39658) and following the final study drug dose in the parent study. Vital signs and urine pregnancy test will have to be performed at the first visit in this study before dosing. MRI and urine pregnancy test results must be available before dosing.

In this study, participants who were in the active double-blind arm in the parent study (WN29922 or WN39658) will continue receiving open-label gantenerumab 510 mg SC Q2W, and those participants who were in the placebo double-blind arm will go through a full uptitration scheme while retaining the blinding to the previous treatment allocation. Details of the dosing scheme are described in Section 4.3.2. If there is a delay in a participant's transition between the OLE part of the parent Study (WN29922 or WN39658) and this study (for instance, due to delays in the approval of this study at a site) that goes beyond a reasonable time frame as determined by the Sponsor, the participant may be asked to start at the dose they were at previously when they completed the parent study and to perform a safety MRI before receiving the target dose. In this case, such decisions will be made after discussion with the Sponsor.

The dosing schedule and the schedule of activities will be different for participants, depending on whether they completed the OLE part of Study WN29922 or WN39658, which covers the uptitration phase for the participants in the placebo arm, or if they completed only the double-blind part. Details are described in Appendix 1.

Following baseline assessments (i.e., OLE Day 1 either in this protocol or in the parent protocol), each participant will be treated for *4* years. *The study duration has been extended from 2 to 4 years in order to collect more information on the long-term safety and tolerability of gantenerumab in AD and its efficacy in the context of long-term exposure and to increase the overall number of participant-years of exposure, thus increasing understanding of gantenerumab's long-term safety and efficacy profiles. Unless participants are eligible and choose to enroll in an alternative gantenerumab OLE study that becomes available,* the final dose of study drug will be administered at OLE Week *206*. At the end of the treatment period, all participants will undergo an OLE Week *208* visit. Participants will be asked to come back for a follow-up visit at OLE Week *220 unless they are transitioning to an alternative gantenerumab OLE study that becomes available.*

Participants who discontinue study drug at any time during this study will be asked to complete an early termination visit 2 weeks after their final dose and also return for collection of safety data (except safety MRI) and limited efficacy data (i.e., secondary endpoints) (see Section 4.6.1).

Participants who do not meet the criteria for participation in this study (screening failure) may be re-screened. The investigator will record reasons for screening failure in the screening log (Section 4.5.1).

3.1.2 Substudies

The substudies associated with Study WN42171 will be described in separate protocols, and participants consenting to enroll in these substudies will be asked to sign the associated Informed Consent Forms. To date, two optional substudies are associated

with Study WN42171: a longitudinal amyloid PET substudy and a longitudinal tau PET substudy.

The amyloid and tau PET assessments will enable a longitudinal evaluation of the effect of gantenerumab on brain amyloid deposition as measured by florbetaben or flutemetamol PET radioligands and tau burden as measured by [^{18}F]GTP1 (Genentech Tau Probe 1; an investigational radioligand for in vivo imaging of tau protein aggregates) in participants with AD.

The collected PET data are expected to help in understanding the effects of gantenerumab on amyloid and tau pathology over time as well as the relationship between changes in florbetaben/flutemetamol/[^{18}F]GTP1-PET and changes in other endpoints in Study WN42171.

Two optional substudies associated with this protocol may be introduced.

In one of them, post-mortem brain tissue may be obtained from participants for evaluation of the effect of long-term gantenerumab therapy on the brain.
The opportunity to donate post-mortem brain tissue may be discussed with participants.

In the other one, digital tools that assess the disease progression of the participants may be tested for validation and for other exploratory purposes.

Interested participants would be provided with additional details. Any further procedures, with respect to the optional substudies, will be governed by a separate consent form and separate substudy protocol document.

3.1.3 Independent Data Monitoring Committee

The iDMC will evaluate participant safety on a regular basis. In addition to the data defined in the iDMC Charter (e.g., the incidence and nature of adverse events, serious adverse events, adverse events of special interest, ARIA-E, ARIA-H, and ISRs), the iDMC will review all necessary cumulative data, including efficacy data if necessary, at regular intervals during the study. It is anticipated that these assessments will occur approximately every 3 months *or as detailed in the iDMC charter*. At the time of each review, the iDMC will make appropriate recommendations (e.g., the study should continue as planned, the safety risk management should be modified, the protocol should otherwise be amended, and enrollment should be held pending further safety evaluations).

Decisions will be made after considering the totality of the available data.
Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details, such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities are detailed in the iDMC Charter.

Final decisions will rest with the Sponsor.

In the event the iDMC which reviews safety in both the parent studies (WN29922 and WN39658) and Study WN42171 is no longer required (for instance after the unblinding of the parent studies) evaluation of participant safety *may* be taken over by the Sponsor's IMC, with details documented in an IMC charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last participant, last visit, occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last participant, whichever occurs later. The end of the study is expected to occur by the end of *2026*.

In addition, the Sponsor may decide to terminate the study at any time.

The total length of this study from baseline visit (OLE Day 1 in either the Study WN42171 protocol or in the parent protocol) to the end of the study (including the follow-up visit) is expected to be approximately *4* years and 3 months. Following uptitration, participants will receive up to *86* doses of gantenerumab 510 mg Q2W. Participants who did not participate in the OLE part of the parent study (WN29922 or WN39658) will also go through an uptitration scheme in the WN42171 study with a duration of at least 34 weeks.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Gantenerumab Dose and Titration Schedule

All participants will receive a target dose of 510 mg gantenerumab SC Q2W, which is the same as the target dose received in the parent Study (WN29922 or WN39658). Participants who will be receiving gantenerumab for the first time in the WN42171 study will follow a titration schedule with a low starting dose and gradual increase in dosing that is expected to reduce the risk of ARIA-E for both apolipoprotein E (*APOE*) carriers and non-carriers, which was also followed in the WN29922 and WN39658 studies.

3.3.2 Rationale for Participant Population

Participants with AD who completed Study WN29922 or WN39658, either the double-blind or OLE part, as applicable, will be eligible to participate in this study in order to evaluate the safety, tolerability, and efficacy of long-term gantenerumab administration. Additionally, participants in the placebo double-blind arm in the parent studies will get exposure to potentially active treatment.

3.3.3 Rationale for Study Treatment Duration

3.3.3.1 *Rationale for the First 2-Year Duration*

In order to collect safety, tolerability, and efficacy data for long-term gantenerumab administration, this study will provide open-label gantenerumab to participants who

completed study WN29922 or WN39658, either its double-blind or OLE part, as applicable, for 2 years starting from baseline (OLE Day 1 in either this protocol or the parent protocol). With the 2-year duration, participants in the placebo double-blind arm in the parent studies (WN29922 or WN39658) will receive the full 2 years of therapy, like their co-participants who were in the active double-blind arm.

3.3.3.2 *Rationale for the Subsequent 2-Year Duration*

The extension of the study treatment duration from 2 to 4 years will allow the collection of more information on the long-term safety and tolerability of gantenerumab in AD and its efficacy in the context of long-term exposure. In addition, this will increase the overall number of participants exposed to gantenerumab and participant-years of exposure, thus increasing understanding of gantenerumab's long term safety and efficacy profiles.

3.3.4 Rationale for ARIA Management Rules

In previous studies with gantenerumab, the Sponsor used the Barkhof scale (Barkhof et al. 2013) to assess the radiological severity of ARIA-E. In this study, the Sponsor plans to use the Bioclinica 5-point scale (Bracoud et al. 2017), which is a simpler scale for assessing ARIA-E severity that is based on a single overall assessment of ARIA-E extent. The Bioclinica 5-point scale is easier for clinicians to use than the Barkhof scale. The Bioclinica scale is commonly used in other clinical trials that are testing anti-amyloid antibodies (Ferrero et al. 2016).

Most cases of ARIA-E occur as an imaging finding alone, without any detectable clinical symptoms (see Gantenerumab Investigator's Brochure safety summary section). As detailed in Appendix 2, ongoing dosing of gantenerumab will occur in cases where ARIA-E is asymptomatic with a low or moderate imaging severity; in such cases, more frequent MRI surveillance (Q4W) will be mandatory. Any ARIA-E associated with symptoms (see definition of symptomatic ARIA-E in Section 5.3.5.2 and Appendix 2), regardless of radiographic severity, will require temporary withholding of study drug administration, until symptoms and ARIA-E findings resolve. The goal, in the context of this carefully controlled study with strict safety monitoring, is to minimize unnecessary study drug interruption, which could itself have a negative impact upon participants. Because of the safety monitoring and the regular review of safety data by the iDMC *or IMC (in the event that the iDMC is no longer required)*, this ARIA management strategy has a neutral impact upon participant risk.

3.3.5 Rationale for Biomarker Assessments

The following biomarker assessments will be used to investigate the effects of gantenerumab on the underlying pathology of AD in the participant population: CSF, plasma, and RNA (Section 4.5.7.3); PET imaging (Section 4.5.11); and brain volumetry, connectivity, and fiber tract integrity (Section 4.5.10).

Exploratory research on potential safety biomarkers may be conducted to support future drug development, including guidance for safety risk management.

3.3.5.1 Cerebral Spinal Fluid Biomarkers

Amyloid plaque deposition, neurofibrillary tangle formation, and neuronal degeneration are known pathologic features of AD. Decreased CSF Aβ1−42 and elevated CSF t-tau and p-tau are considered a biochemical signature of AD. Accumulating evidence suggests that low CSF Aβ1−42 reflects underlying amyloid plaque pathology, whereas increased t-tau and p-tau levels may be reflective of neurodegeneration and/or tau pathology. Amyloid deposition may be the initiating event in the cascade of pathologic processes underlying AD, whereas tau pathology appears to be a subsequent event and more associated with neurodegeneration. Therefore, t-tau and p-tau may be studied as downstream biomarkers of the primary target of anti-amyloid therapies such as gantenerumab.

Although biomarkers indicative of certain neuropathologies have not yet been validated as surrogate markers for clinical efficacy, there is some evidence that anti-Aβ treatments may cause changes in these biomarkers. A neuropathologic study of patients with AD (Study AN1792) suggests that active amyloid immunotherapy ameliorates neurite abnormalities and tau pathology through decreased tau phosphorylation (Serrano-Pozo et al. 2010). In a pooled analysis of CSF data from two Phase II trials with bapineuzumab in patients with mild to moderate AD, a decrease in both p-tau and t-tau levels relative to baseline was observed in the bapineuzumab group after 12 months of therapy (Blennow et al. 2010). These findings were confirmed in two Phase III studies with bapineuzumab (Sperling et al. 2012) as well as in Study WN25203 with gantenerumab. In Study WN25203, CSF biomarkers were analyzed over the 2-year period for changes in multiple proteins, including $A\beta_{1\text{-}42}$, t-tau, p-tau, and neurogranin. Markers of neurodegeneration were significantly reduced in the 225-mg gantenerumab group compared with placebo over 2 years, with greater relative reduction in p-tau relative to t-tau. The greatest effect was reduction in p-tau in the 225-mg gantenerumab arm at 2 years relative to the change in the placebo arm. There was no treatment effect on CSF $A\beta_{1-42}$ (Nikolcheva et al. 2015). Because no evidence of efficacy has been demonstrated with these therapies in clinical trials yet, changes in these biomarkers provide meaningful information about the PD effects of gantenerumab and the effect on pathologic processes underlying AD.

Based on these data and on the proposed mechanism of action of gantenerumab, levels of CSF t-tau and p-tau and additional exploratory biomarkers reflecting neurodegeneration will be assessed in this study. Because gantenerumab is expected to clear amyloid from the brain, levels of CSF $A\beta_{1-42}$ will also be measured.

3.3.5.2 Brain Volumetry, Connectivity, and Fiber Tract Integrity

A characteristic feature of AD is neuronal destruction. Such neuronal loss is demonstrated at a macroscopic level by progressive cerebral atrophy, which can be

tracked on MRI (Fox and Kennedy 2009). Multiple changes in brain anatomy beyond those associated with normal aging have been reported in patients with AD (e.g., enlarged ventricles, decreased cortical thickness, decreased total brain volume, and hippocampal atrophy), and there is evidence for strong correlations between these imaging biomarkers and functional cognitive measures (Li and Wahlund 2011). Based on volumetric MRI measurements, the two most established markers of disease progression in longitudinal observational studies are hippocampal and whole brain atrophy (Fox et al. 2000, 2005; Jack et al. 2010), with ventricular expansion a related quantitative marker.

Therefore, to quantify the effects of gantenerumab on neurodegeneration, whole brain volume, ventricular enlargement, and regional brain volume changes will be assessed in this study. All MRI reads and volume measures will be conducted by the central reader.

In addition to the structural brain volume changes, changes in brain functioning of participants will be assessed using a blood oxygenation level-dependent (BOLD) resting-state functional MRI (rs-fMRI) procedure (at sites where this procedure is available) with a paradigm-free procedure (Grecius et al. 2004; Filippi and Agosta 2011). Increased concentrations of Aβ in the brains of patients with AD contribute to neuronal degeneration in the brain over time and have been associated with reduced functional connectivity of various brain networks using rs-fMRI (Sheline et al. 2010; Binnewijzend et al. 2012; Brier et al. 2012; Sheline and Raichle 2013). Resting-state functional connectivity has been found to be decreased in brain regions such as the hippocampus, the default mode network (regions such as precuneus, anterior cingulate, and parietal and temporal cortices), and cortical regions in which the functional connectivity is continuously decreased as disease progresses. It has also been found to be decreased in cognitively normal elderly patients with brain amyloid deposition (Pittsburgh Compound-B+PET scans). Alteration of the decreased brain functional connectivity has been shown using therapeutic interventions such as memantine (Lorenzi et al. 2011) or donepezil in patients with AD (Goveas et al. 2011; Solé-Padullés et al. 2013). Increased brain functional connectivity was found after just 3 months of treatment with donepezil, which correlated with changes in cognitive measures such as the ADAS-Cog (Goveas et al. 2011; Solé-Padullés et al. 2013). Therefore, therapeutic interventions, which act to remove Aβ from the brains of patients with AD, may help to reverse the altered functional connectivity presumably caused by the accumulation of Aβ in the brain.

The integrity of white matter tracts will be assessed prior to and after treatment with gantenerumab using diffuse tensor imaging (DTI)-MRI techniques. DTI-MRI is based on the measurement of diffusion properties of water molecules in the axonal fiber tracts in white matter. Whereas water molecules can diffuse isotropically in CSF, they are restricted axially in white matter bundles. Widespread group differences in the degree of anisotropic diffusion, or fractional anisotropy (FA), has been seen between patients with AD and healthy subjects (Jack et al. 2015). Greater FA values are thought to indicate

greater white matter integrity. Likewise, mean diffusivity, which measures the average rate of diffusion in all directions, has been shown to be higher in groups with AD compared with healthy controls, presumably owing to increased white matter injury in patients with AD (Nir et al. 2013).

At sites having the required software and hardware, rs-fMRI (BOLD rs-fMRI) and DTI-MRI will be performed when feasible during the same scanning session as the structural MRI to assess functional brain connectivity and fiber tract integrity.

3.3.6 Rationale for Pharmacokinetic Sampling

A sparse sampling schedule is being utilized to minimize participant burden while providing an adequate characterization of the population PK profile of gantenerumab. The PK data may be combined with available data from other gantenerumab studies and may be used to assess exposure–response relationships for relevant imaging, CSF, plasma PD biomarkers, ECGs, and efficacy and safety outcomes in participants with AD, as appropriate.

4. MATERIALS AND METHODS

4.1 PARTICIPANTS

Any participant who has completed Study WN29922 or WN39658, either the double-blind or OLE part, as applicable, can be enrolled in this study if they meet the inclusion/exclusion criteria set out below. This should lead to no more than 2032 participants with AD enrolled in Study WN42171, dependent on the number of eligible participants completing the parent Studies (WN29922 and WN39658) and who consent to Study WN42171.

4.1.1 Inclusion Criteria

Participants must meet the following criteria for study entry:

- Signed Informed Consent Form by the participant with AD and/or the legal authorized representative as per local requirements
- Completed Study WN29922 or WN39658, either its double-blind part (participants have reached the 510 mg Q2W dose schedule by the time of completion) or OLE part (participants have received at least 3 doses of 510 mg Q4W), and did not discontinue study drug early
- Ability to comply with the study protocol
- Willingness and ability to complete all aspects of the study (including MRI).
- The participant should be capable of completing assessments either alone or with the help of the caregiver.
- Availability of a person (referred to as the “caregiver” throughout this protocol) who:
  - In the investigator’s judgment, has frequent and sufficient contact (e.g., 5 times per week or approximately 10 hours per week) with the participant

- In the investigator's judgment, is able to provide accurate information regarding the participant's cognitive and functional abilities, including knowledge about domestic activities, hobbies, routines, social skills, and basic activities of daily life; work and educational history; cognitive performance including memory abilities, language abilities, temporal and spatial orientation, judgment and problem solving; emotional and psychological state; and can report any changes in the general health status
- Agrees to provide information and to complete all aspects of the study at clinic visits (which require partner input for scale completion)
- Signs the necessary Informed Consent Form(s), and has sufficient cognitive capacity to accurately report on the participant's behavior as well as cognitive and functional abilities
- Is fluent in the language used at the site and has sufficiently good general health to have a high likelihood of maintaining the same level of interaction with the participant and participation in study procedures throughout the duration of the study

  Every effort should be made to have same caregiver participate throughout the duration of the study.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception as defined below:
  - Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for at least 16 weeks after the final dose of gantenerumab.
  - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.
  - Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- Agreement not to donate blood or blood products for transfusion for the duration of the study and for 1 year after final dose of study drug.

4.1.2 Exclusion Criteria

Participants who meet any of the following criteria will be excluded from study entry:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within at least 16 weeks after the final dose of study drug

  Women of childbearing potential must have a negative urine pregnancy test at the final visit of the parent study.
- Prematurely discontinued from Study WN29922 or WN39658, either its double-blind or OLE part, as applicable, or from study drug, for any reason
- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Received any investigational treatment other than gantenerumab during or since completion of Study WN29922 or WN39658, either its double-blind or OLE part, as applicable
- Evidence of disseminated leptomeningeal hemosiderosis (i.e., more than three focal leptomeningeal hemosiderosis)
- Evidence of intracerebral macrohemorrhage
- Use of prohibited medication (see Section 4.4.2)
- Evidence of ARIA-E on the last MRI scan report in Study WN29922 or WN39658, either its double-blind or OLE part, as applicable

  Participants should remain in the parent study, as governed by that protocol, and may enroll in this study once the ARIA-E is resolved.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a non-randomized, open-label study. An interactive voice or web-based response system (IxRS) will be used to manage participant enrollment and drug supply. After initial written informed consent has been obtained the study site may obtain the participant's identification number. After all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's treatment assignment from the IxRS.

Participants randomized to the active treatment arm in the parent study (WN29922 or WN39658) will continue to be administered the study drug every 2 weeks (Q2W administration of 510 mg SC gantenerumab). Participants randomized to the placebo arm in the parent study (WN29922 or WN39658) will have to go through at least 34 weeks of uptitration. Participants, sites, and Sponsor will remain blinded to previous treatment allocation in the parent study (WN29922 or WN39658) to protect study integrity.

4.2.2 Blinding

To protect study data integrity and to aid the assessment of the long-term effects of gantenerumab, study site personnel and participants will be blinded to previous treatment assignment in the parent studies (WN29922 or WN39658). The Sponsor and its agents will also be blinded to previous treatment assignment, at least until unblinding of the parent studies (WN29922 and WN39658), which will happen while this study is ongoing, with the exception of individuals who require access to participant's treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, operational assay group personnel, IxRS service provider, and iDMC members.

Pharmacokinetics and immunogenicity samples will be collected from all participants, regardless of the treatment assignment. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to participants' treatment assignments. Baseline immunogenicity samples will be analyzed for all participants.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which participant management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly.
The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to participant unblinding, the investigator will be able to break the treatment codes by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment assignment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The participant may continue to receive treatment, and the investigator, participant, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to participant treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is gantenerumab.

4.3.1 Gantenerumab and Placebo

The Sponsor will supply gantenerumab and placebo, as required for the uptitration period, as liquid formulation ready for SC administration. Packaging of the study drug will be overseen by the Roche Clinical Trial Supplies Department and will bear a label with the identification required by local law, the protocol number, study drug identification, and dose. The packaging and labeling will be in accordance with Roche standard and local regulations. Upon receipt of the investigational products at the site, site personnel should check the product for damage and verify the proper identity, quantity, and integrity of the study drug. Site personnel should report any deviations or product complaints to the monitor upon discovery. For further details, please refer to the Gantenerumab Investigator's Brochure.

For information on the formulation and handling of gantenerumab, see the pharmacy manual and the Gantenerumab Investigator's Brochure.

4.3.2 Study Treatment Dosage, Administration, and Compliance

During the WN42171 study, participants previously randomized to the active treatment arm and those who were previously randomized to placebo and have completed OLE uptitration in the parent study (WN29922 or WN39658) will continue to be administered the study drug every 2 weeks (Q2W administration of 510 mg SC gantenerumab). Participants previously randomized to the placebo arm who did not participate in the OLE part of the parent study (WN29922 or WN39658) will be required to undergo the uptitration scheme of 34 weeks. Participants who completed the OLE part of the parent study (WN29922 or WN39658), will continue the schedule of activities as per their OLE Day 1 visit in the parent study (WN29922 or WN39658).

In order to maintain the previous study treatment blinding (the Sponsor, investigator, and participant), all participants will be dosed every 2 weeks as illustrated in Table 1 . A safety MRI should be performed before each uptitration to ensure the participant can be safely uptitrated to the next dose.

To ensure blinding to previous treatment, IMP will be administered as one 0.8-mL and two 1.7-mL injections for the 120-mg dose or as two 1.7-mL injections for the 255-mg dose and 510-mg dose, respectively, SC to the abdomen. Injections may contain active gantenerumab or placebo to ensure the correct total dose of active gantenerumab at each visit (see Table 1). Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Note: A minimum of 3 doses during each dosing step must be administered before the participant is eligible for uptitration, subject to the results of a pre-uptitration safety MRI. **A dose is defined as two consecutive dosing visits (one with an odd dose number and one with an even dose number,** see Table 1). A participant may still be eligible for uptitration even if these requirements are not met, provided that they have been administered IMP at 3 odd dosing visits at a given dose level (see Table 1).

After OLE Week 34 (i.e., beyond the time frame considered in Table 1), all participants who have completed the uptitration will receive two 1.7-mL injections of active gantenerumab for the 510-mg dose at each subsequent 2-week visit.

At applicable sites, study treatment may be administered by a trained nursing professional at the participant's home or another suitable location, if the participant has given written informed consent to participate in home nursing visits.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error along with any associated adverse events should be reported as described in Section 5.3.5.13.

Guidelines for treatment interruption or discontinuation for participants who experience selected adverse events are provided in Section 5.

Table 1 Gantenerumab Dosing Design for Participants Who Did Not Participate in the OLE Part of the Parent Study (WN29922 or WN39658)

Visit		OLE Day 1	OLE Wk 2	OLE Wk 4	OLE Wk 6	OLE Wk 8	OLE Wk 10	OLE Wk 12	OLE Wk 14	OLE Wk 16	OLE Wk 18	OLE Wk 20	OLE Wk 22	OLE Wk 24	OLE Wk 26	OLE Wk 28	OLE Wk 30	OLE Wk 32	OLE Wk 34
Dose Number Within Study WN42171		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Participants previously on placebo	Dose	120 mg Q4W						255 mg Q4W						510 mg Q4W					
	Injections (mL)	1× 0.8A + 2× 1.7P	1× 0.8P + 2× 1.7P	1× 0.8A + 2× 1.7P	1× 0.8P + 2× 1.7P	1× 0.8A + 2× 1.7P	1× 0.8P + 2× 1.7P	1× 1.7A + 1× 1.7P	2× 1.7P	1× 1.7A + 1× 1.7P	2× 1.7P	1× 1.7A + 1× 1.7P	2× 1.7P	2× 1.7A	2× 1.7P	2× 1.7A	2× 1.7P	2× 1.7A	2× 1.7P
Participants previously on active	Dose	510 mg Q2W																	
	Injections (mL)	2× 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A

A = active treatment; OLE = open-label extension; P = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; Wk = week.

4.3.3 PET Tracers

All participants who are enrolled in the PET substudies will be assessed by PET imaging using the same PET ligand as per the parent study (florbetaben or flutemetamol for the amyloid PET and [^{18}F]GTP1 for the tau PET substudy). According to European Union (E.U.) guidance, the PET tracers, as used in the context of this study, are designated as non-IMP. In some regions, according to local regulations, these PET tracers may be considered to be IMP.

In countries where the PET radioligands are approved for marketing, the approved local product information will be provided, and in countries where they are not approved for marketing, the Investigator's Brochures will be provided.

For the safety reporting requirements dealing with the PET tracers used in this study please refer to Section 5.7.

4.3.4 Investigational Medicinal Product Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.5 Continued Access to Gantenerumab

The Sponsor will offer continued access to Roche IMP gantenerumab free of charge to eligible participants in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A participant will be eligible to receive Roche IMP gantenerumab after completing the study if all of the following conditions are met:

- The participant has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being.
- There are no appropriate alternative treatments available to the participant.
- The participant and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A participant will not be eligible to receive Roche IMP gantenerumab after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the participant's country and is reasonably accessible to the participant (e.g., is covered by the participant's insurance or wouldn't otherwise create a financial hardship for the participant).
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for AD.
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for AD
- Provision of the Roche IMP is not permitted under the laws and regulations of the participant's country.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a participant in addition to protocol-mandated treatment from 3 months prior to first administration of study drug in Study WN42171 to the OLE final follow-up visit. All such medications (including name, dose, administration schedule, start and end dates) used by the patient during Study WN42171 should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Participants are eligible for study participation whether or not they are receiving approved medication for AD (i.e., AChEIs, memantine, and/or medical food supplements, where approved) with the exception of GV-971. Participants who have received GV-971, are currently receiving GV-971 or who are planning to receive GV-971 during the study are not eligible. Information about background AD medication (e.g., drug name, dose, and start and stop dates, reason for interruption or modification) should be captured on the eCRF.

Adding a new medication or changing the dose of a medication during the study should occur only for the treatment of an adverse event or in case of AD progression. Whenever possible, a medication listed below should be used if appropriate.

The following medications are permitted. Doses are expected to remain stable after baseline:

- Anticonvulsant medications
- Selective serotonin reuptake inhibitors for the treatment of depressive symptoms

- Over-the-counter and/or herbal medications, food additives, or any other agent or supplement intended to improve cognition or reduce cognitive decline
- Medications used to treat a mood or anxiety disorder given as maintenance treatment (with the exception of benzodiazepine)
- Use of short-acting (non-extended release) opioid medications for pain
- Use of benzodiazepines, including alprazolam, lorazepam, oxazepam, triazolam, or temazepam, or short-acting hypnotic medication (e.g., zolpidem)
- A dose of benzodiazepine for pre-surgical and pre-imaging sedation at appropriate visits if allowed by the Ethics Committee (EC) or Institutional Review Board (IRB)
- Use of centrally acting antihistamine medications
- Under certain circumstances, initiation of anti-hemostasis medications during the study conduct

Anticoagulation therapy lasting no longer than 3 weeks (e.g., temporary usage during surgery) is permitted. However, for any such use it is recommended to prospectively seek advice from the Medical Monitor, and study drug *should be temporarily interrupted whilst anticoagulation therapy is ongoing.*

Participants who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

The administration of COVID-19 vaccines, just as with other vaccinations (e.g., influenza) will be considered as a concomitant medication. Based on the available information, no interactions between gantenerumab or PET tracers and the COVID-19 vaccines are expected to occur, and no other safety concerns have been identified that would prohibit the vaccination of participants enrolled in the studies where gantenerumab is being investigated for the treatment of AD. However, the published safety data for COVID-19 vaccines show that overlapping adverse events between medicines such as gantenerumab and the vaccine can occur: the timing and the nature of local injection reactions (occurring within 24 hours) as well as of systemic injection reactions may be similar for both products. To facilitate the correct clinical assessment of any adverse events and to continue correct attribution of adverse events related to study drugs (gantenerumab and PET tracers) or to the vaccination, namely of local and systemic reactions following the injections, the Sponsor recommends to vaccinate study participants at least 24–48 hours after an injection of study drug. Similarly, vaccination in the 48 hours preceding a study drug administration should also preferably be avoided. However, the timing of the study visits and study drug administration should not be unduly postponed because of a vaccination.

4.4.2 Prohibited Therapy

The following medications are prohibited at study start and during the entire period of study participation. Participants who start these medications during the study may be withdrawn from study treatment:

- Any active immunotherapy (vaccine) that is being evaluated to prevent or postpone cognitive decline
- Any passive immunotherapy (immunoglobulin) or other long-acting biologic agent that is under evaluation or approved to prevent or postpone cognitive decline within 1 year of screening, except for gantenerumab
- Any other investigational treatment or any other treatment with an investigational monoclonal antibody within 5 half-lives or 4 months prior to screening, whichever is longer
- Any previous administration of GV-971
- Anti-coagulation medications
  - Anti-platelet treatments (e.g., aspirin, clopidogrel, and dipyridamol) are permitted.
  - Short-term, perioperative use of anticoagulant medications will not result in permanent discontinuation from the study; however, for any such use, it is recommended to prospectively seek advice from the Medical Monitor and *study drug should be temporarily interrupted whilst anticoagulation therapy is ongoing.*

The following medications *should preferably be avoided* in this study *although they* are *not strictly prohibited*:

- Stimulant medications (amphetamine, methylphenidate preparations, or modafinil) throughout the study
- Typical antipsychotic or neuroleptic medication
- Atypical antipsychotic medications
- Chronic use of opiates or opioids (including long-acting opioid medication)
- Chronic use of benzodiazepines, barbiturates, or hypnotics

If possible, use should be limited to intermittent short-term use. Consideration should be made as to whether clinically appropriate to interrupt the medication 2 days or at least 5 half-lives (whichever is longer) prior to any neurocognitive assessment due to their psychoactive effects.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each participant.

At applicable sites, certain study assessments may be performed by a mobile nursing (MN) professional at the participant's home or another suitable location, such as a nursing center, to improve access and convenience for participants participating in the study. The Sponsor will select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a participant and the participant gives written informed consent to participate in MN visits, the MN network will communicate with the participant and the participant's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. The schedule of activities (see Appendix 1) specifies the assessments that may be performed by an MN professional.

4.5.1 Informed Consent Forms and Screening Log

Informed consent should be obtained from participants while they are in the parent study (WN29922 or WN39658) including in the safety follow up, until a day before the first dose in the study WN42171. In special situations, informed consent can be obtained at a later timepoint upon providing an appropriate rationale to the Sponsor. Written informed consent for participation in the study must be obtained before performing any study-related procedures. Informed Consent Forms for enrolled participants and for participants who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that participants meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Baseline Definition and Assessments

For participants who completed the double-blind part and did not enter the OLE part of study WN29922 or WN39658: The first dosing visit in this study will be considered as baseline (OLE Day 1), and the final efficacy and safety visit assessment of the parent Study (WN29922 or WN39658) will be considered as baseline assessment if occurring within a specific timeframe.

For participants who completed the double-blind part and the OLE part of study WN29922 or WN39658: the baseline visit will be the OLE Day 1 visit of the parent study (WN29922 or WN39658). This group of participants will roll over to study WN42171 upon the completion of their uptitration. The first visit in this study should take place approximately 2 weeks after the OLE Week 34 visit or the last dose visit in the parent study (WN29922 or WN39658) OLE.

On the day of the first dose of gantenerumab in study WN42171, if results of standard-of-care tests or examinations (coagulation, ECG, serum chemistry, and hematology; complete physical examination) performed within 4 weeks are available, they do not have to be repeated. For C-SSRS, and cognitive scale results, the time interval is 6 months. MRI scan does not need to be repeated if performed within 6 months in the parent study and following the final study drug dose in the parent study. Vital signs, urine pregnancy test for women of childbearing potential, collection of adverse events, and review of concomitant medications have to take place before each dose administration. The MRI can only be used if it was the last prescribed per-protocol MRI in the parent study, including those required for ARIA-E follow up.

4.5.3 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history and demographic data as collected in the parent Study WN29922 or WN39658 will be used in this study and should include clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse. Medical history and demographic data will be automatically transferred into the study WN42171 eCRF. In addition, ongoing concomitant medications will automatically be transferred from the parent study (WN29922 or WN39658) to study WN42171. All changes to medications during the study (e.g., prescription drugs, over the counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) should be recorded in the eCRF. Changes in medical history will be collected once after completion of the double-blind part in the parent study (WN29922 or WN39658) and before OLE Day 1 either in the parent study or in study WN42171.

Demographic data will include age, sex, and self-reported race/ethnicity.

Because this study is being conducted in multiple geographic regions, it is likely that participants of different ethnic origins will be enrolled in the study. Although there is currently no indication that gantenerumab is metabolized or eliminated differently or that the treatment effect would be different in participants of different ethnic origins, collecting this information is essential to adequately evaluate the results of this study (e.g., possible differences in PK exposure [concentration of the drug in the blood] or treatment effect).

4.5.4 Physical Examinations

A complete physical examination, performed at specified visits as per the schedule of activities (Appendix 1), should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated. Conditions reported as part of the medical history or adverse events in the parent study do not need to be re-entered.

Limited, symptom-directed physical examinations should be performed at specified visits and as clinically indicated. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

In addition, weight will be obtained at OLE Day 1, at OLE Week 104*, at OLE Week 208,* or at the OLE early termination visit, at every visit at which creatinine clearance is tested, and at any other visit as deemed necessary by the investigator. Height will be obtained at the first dosing visit only.

The physical examination does not have to be repeated at OLE Day 1 or at the first dosing visit in the WN42171 study if the last examination performed in the parent study (WN29922 or WN39658) occurred within the previous 4 weeks.

4.5.5 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure while the participant is in a seated position, and temperature. Any abnormalities recorded in the parent studies do not need to be re-entered on the Study WN42171 eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements.

Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

Vital sign measurements may be performed by an MN professional.

4.5.6 Cognitive, Functional, and Health Economics Assessments

The assessments described in this section will be performed as outlined in the schedule of activities (see Appendix 1) and in the order specified in Section 4.5.6.14.

Whenever possible, there should be consistency in the rater and caregiver who complete the scales for each participant throughout the duration of this study and also between this study and the parent study. Potential raters will receive training and be approved by the rating scale contract research organization prior to being allowed to administer any cognitive assessments or rating scales in the study.

Whenever possible, cognitive and functional assessments should be performed at the visit timepoints indicated in the schedule of activities (see Appendix 1). However, in exceptional circumstances, if the caregiver, the primary rater, or even the participant

cannot perform these assessments as per the schedule of activities, they may be performed up to 4 weeks out of window.

Given that the CDR, a secondary efficacy outcome measure in this trial, involves subjective judgment, the adequacy of participant and caregiver interviews and ratings will be monitored by an endpoint reliability program administered by the rating scale vendor. This is considered an essential part of good research methodology. For CDR as well as for some other scales, audio recordings may be used for quality assurance purposes. Prior studies have clearly demonstrated that the failure to adequately monitor such ratings can substantially increase the risks of failed trials (Becker and Greig 2008; Kobak 2010).

During OLE Day 1 or the visit of the first study drug administration in Study WN42171, scale assessments do not have to be repeated if the last assessments performed in the parent study WN29922 or WN39658 occurred within 6 months.

4.5.6.1 Clinical Dementia Rating Scale

The CDR–Global Score (CDR-GS) characterizes a participant's level of impairment according to the following categories: 0 (normal), 0.5 (very mild dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia). The CDR–Sum of Boxes (CDR-SOB) score is a detailed quantitative general index that provides more information than the CDR-GS in participants with mild dementia (Berg 1988; Morris et al. 2001, O'Bryant et al. 2010) and is scored from 0–18 with higher scores indicating greater impairment. The CDR characterizes six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The necessary information to make each rating is obtained through a semi-structured interview with the participant and a reliable informant or collateral source (e.g., a caregiver).

As much as is feasible, the CDR should be administered to an individual participant by the same assessor throughout the study, preferably the same assessor as in the parent study, and that assessor should not perform the MMSE, ADAS-Cog, Verbal Fluency Task, Coding, FAQ, or ADCS-ADL. However, if in exceptional circumstances only this assessor is available to perform these other scales, then the CDR participant interview must be completed after the caregiver interview but before ADAS-Cog, MMSE, Verbal Fluency Task, Coding, and other scales are completed. Nevertheless, on OLE Day 1, on OLE Week 52, on OLE Week 104*, on OLE Week 156, and on OLE Week 208,* the CDR rater cannot perform other scales than the CDR. In addition, the CDR rater should not be involved in safety assessments and especially should not receive information about any ARIA findings.

4.5.6.2 Alzheimer's Disease Assessment Scale-Cognitive Subscale

The ADAS-Cog is the most frequently used scale to assess cognition in clinical trials for mild to moderate AD dementia (Rozzini et al. 2007; Connor and Sabbagh 2008;

Ihl et al. 2012). More specifically, the ADAS-Cog is a participant-based assessment that measures learning and memory, language production, language comprehension, constructional praxis, ideational praxis, and orientation. The modified version will be used; it has 13 items and includes the addition of delayed word recall and a number of cancellation subtests, as well as use of only one trial for word recognition (Mohs et al. 1997). Equivalent alternate forms of the word recall, word recognition, and number cancellation subtests will be used in successive test administrations.

4.5.6.3 Mini-Mental State Examination

The MMSE is a set of standardized questions used to evaluate possible cognitive impairment and help stage the severity level of this impairment (Folstein et al. 1975). The questions target six areas: orientation, registration, attention, short-term recall, language, and constructional praxis/visuospatial abilities. The MMSE is a participant-based assessment.

4.5.6.4 Verbal Fluency Task

The category verbal fluency (e.g., animals) is a participant-based assessment that measures speed and flexibility of verbal thought. Verbal fluency tests are sensitive tools for detecting dementia (Pasquier et al. 1995; Lezak et al. 2004) and for monitoring decline over time (Clark et al. 2009).

4.5.6.5 Coding

The Coding, also called Digit Symbol Substitution Test (or DSST), is a subtest from the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV; Wechsler 2008). The Coding is a participant-based assessment that measures speed of processing and associative memory. The test is known to be sensitive to disease progression (Lezak et al. 2004). The 120-second version of the test will be used in this study.

4.5.6.6 Functional Activities Questionnaire

The FAQ (Pfeffer et al. 1982) is an informant-based measure of functional abilities. Informants provide performance ratings of the target person on ten complex higher-order activities.

4.5.6.7 Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory

The ADCS-ADL (Galasko et al. 1997) is the scale most widely used to assess functional outcome in participants with AD (Vellas et al. 2008). The ADCS-ADL is a 23-item informant-based questionnaire that covers both basic activities of daily living (ADL) (e.g., eating and toileting) and more complex ADL or instrumental ADL (e.g., using the telephone, managing finances, preparing a meal). It has a 4-week recall period. Total scores range from 0–78, with higher scores indicating better functioning.

4.5.6.8 Zarit Caregiver Interview for Alzheimer's Disease

ZCI-AD is a modified version of the Zarit Burden Interview, which was originally designed to reflect the stresses experienced by caregivers for people with dementia

(Zarit and Zarit 1990). The modified version includes slight modifications in item and title wording (e.g., removal of "your relative" to refer directly to the participant, removal of "burden" from title) and the use of 11-point numerical rating scales. The ZCI-AD scale consists of 30 items and is completed by the caregiver without involvement from the site staff. It has a 4-week recall period.

4.5.6.9 Quality of Life–Alzheimer's Disease

The QoL-AD was developed to assess quality of life (QoL) in participants who have dementia (Logsdon et al. 1999, 2002). The QoL-AD consists of 13 items covering aspects of participants' relationships with friends and family, physical condition, mood, concerns about finances, and overall assessment of QoL. The total score is the sum of the 13 items and ranges from 13–52, with higher scores indicating better health-related QoL. In this study, the QoL-AD will be administered in a standardized, structured interview format to participants by investigative staff in order to gather participant responses about QoL. The caregiver will also complete the caregiver version of the questionnaire to enable proxy responses from the caregiver.

4.5.6.10 EQ-5D

The EQ-5D is a standardized measure of health status designed to provide a simple generic measure of health for clinical and economic appraisal. It is broadly applicable across a wide range of health conditions and treatment.

The EQ-5D assesses five domains to provide a health state index. These are anxiety/depression, pain/discomfort, usual activities, mobility, and self-care.

The following two versions will be used in this study:

- EQ-5D-5L Proxy, Version 1: The caregiver (the proxy) is asked to rate the participant's health-related QoL in his or her (the proxy's) opinion.
- EQ-5D-5L, Self-Complete Version: The caregiver is asked to rate his or her own health-related QoL.

4.5.6.11 Resource Utilization in Dementia Scale

The RUD scale (Wimo et al. 2003) aims to document formal and informal resource use in a clinical trial setting. The RUD-Lite captures the most important elements in dementia care: accommodation, informal care, hospitalizations, and community care services. Information on caregiver sociodemographics in addition to working status and effect on productivity will be collected. The amount of informal care will be collected according to three types of care: personal ADL, instrumental ADL, and supervision. Data on accommodation and temporary changes in accommodation during the last month and the duration of these will be collected according to four levels of accommodation: own home, intermediate forms of accommodation, dementia-specific residential accommodation, and nursing home. Resource utilization will be recorded as the number of nights spent in different types of hospital wards, the number of visits to the

most common types of outpatient care, and the number of visits in community care services.

4.5.6.12 Neuropsychiatric Inventory Questionnaire

The NPI-Q (Kaufer et al. 2000) was developed to assess a wide range of behaviors encountered in patients with dementia, to provide a means of distinguishing severity of behavioral changes, and to facilitate rapid behavioral assessment through the use of screening questions. It is an informant-based instrument in which 12 behavioral domains are evaluated. The recall period is the past month, and severity scores range from 0–36, with higher scores indicating greater severity. The caregiver's distress portion of the scale will not be used in this study.

4.5.6.13 Electronic Assessment of Rating Scales

The following rating scales will be captured electronically and transferred to the database directly from the core laboratory: ADAS-Cog, Verbal Fluency Task, ADCS-ADL, CDR, MMSE, FAQ, QoL-AD, EQ-5D, RUD-Lite, NPI-Q, $ZCI\text{-}AD,$ and CSSR-S.

4.5.6.14 Treatment Period Assessments

The recommended order of assessments and rating scales is as follows:

- Clinical assessments (e.g., CDR, MMSE, and ADAS-Cog), including all those that require caregiver input, should be completed before any invasive safety assessments.
- Vital sign measurements, physical examination, ECGs, blood draws for clinical laboratory assessments, PK, ADA, plasma biomarker sampling, and urine samples are recommended to be conducted following scale assessments and must be performed prior to study drug administration.

The recommended order of clinical assessments/rating scales at baseline is as follows:

Participant Assessments	Caregiver Assessments
1. ADAS-Cog13 2. CDR (participant interview) 10-min break (optional) 3. MMSE 4. Coding 5. Verbal Fluency Task 10-min break (optional) 6. QoL-AD 7. C-SSRS	1. CDR (caregiver input) 2. FAQ 3. ADCS-ADL 4. ZCI-AD 5. QoL-AD 6. EQ-5D 7. RUD-Lite 8. NPI-Q

ADAS-Cog13 = Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living; CDR = Clinical Dementia Rating; C-SSRS = Columbia–Suicide Severity Rating Scale; EQ-5D=EuroQol-5-Dimension Questionnaire; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; NPI-Q = Neuropsychiatric Inventory–Questionnaire; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; ZCI-AD = Zarit Caregiver Interview for Alzheimer's Disease.

If assessments are split over 2 days, all safety assessments must be performed on the same day as the study drug administration.

On each dosing day, after all assessments prior to dosing have been completed (see the schedule of activities in Appendix 1), gantenerumab and matching placebo where applicable during uptitration will be administered SC at room temperature.

For participants who completed the double-blind part and did not enter the OLE part of parent Study (WN29922 or WN39658): Participants should be observed for a minimum of 2 hours for the first eight administrations. Starting at the ninth administration, participants should be observed for a minimum of 1 hour.

For participants who completed the double-blind part and the OLE part of parent Study (WN29922 or WN39658): Participants should be observed for a minimum of 1 hour.

Participants should leave the study center after injections only if they appear to be tolerating the injections. When doses are to be administered remotely from the clinical sites, study drug administration may be performed only by qualified health care providers, as defined by local regulations, who must remain with the participants for a minimum of 1 hour after each injection and be equipped with rescue medications.

Rescue medications to treat anaphylactic and anaphylactoid reactions must be available at the site or at the dosing location for HN visits. Participants and their caregivers will be

alerted to watch for signs of anaphylactic and anaphylactoid reactions and to contact the study center as soon as possible if any such signs are noted.

Visits at which the participant receives study drug may take place within ±3 days of the protocol-specified date in the schedule of activities (Appendix 1). It is recommended not to administer more than 2 dosing visits (e.g., 2×510 mg Q2W) within 28 days. At every visit, participants should return to the initial planned visit schedule defined as per the baseline visit (OLE Day 1).

All visits should be scheduled as close as possible to the exact day. It is preferred that all assessments for a visit be performed on the same day, but, if necessary, assessments may be performed over more than one day. Preferably, all clinical scales and assessments should be performed on the same day. Study drug administration should be performed only after all assessments and rating scales for the participant have been completed.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent for analysis:

- Serum chemistry panel: AST, ALT, ALP, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, serum creatinine (and creatinine clearance calculated by the central laboratory). Hemoglobin A_{1c} (HbA_{1C}), glucose, insulin, C-reactive protein, folic acid, and vitamin B-12 will also be assessed according to the schedule of activities (Appendix 1).
- Coagulation: prothrombin time
- Thyroid function testing: thyroid-stimulating hormone, thyroxine (T4), and free T4
- Lipids: cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides
- Hematology: WBC count, RBC count (with morphology), hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Urinalysis

  At the OLE Day1 visit or at the visit of the first study drug administration in Study WN42171, if deemed necessary by the investigator, urinalysis may be performed at the site by dipstick for blood, protein, glucose, and pH. Microscopic examination will be performed by the central laboratory if blood and/or protein results are positive or strongly positive.
- Urine pregnancy test

  Urine pregnancy tests will be performed at each dosing visit (prior to dose administration) and at the safety follow up visit for women of childbearing potential (including those who have had a tubal ligation) and at the site for any other female participants if required by local regulations. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory.

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

During the OLE Day 1 visit or at the visit of the first study drug administration in Study WN42171, the above laboratory assessments (excluding urine pregnancy test) do not have to be repeated if the last assessments performed in the parent studies WN29922 or WN39658 occurred within 4 weeks.

4.5.7.1 Pharmacokinetic Samples

Plasma Samples

Blood samples will be collected to evaluate the pharmacokinetics of gantenerumab in plasma as noted in the schedule of activities (see Appendix 1).

An additional PK sample for the assessment of plasma concentrations of gantenerumab will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study

visit) once the site becomes aware of the occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria.

Samples will not be analyzed in real time but will be batched for analysis throughout the study.

Unused sample material may be used for the purpose of current gantenerumab assay improvement and for the quantification of specific gantenerumab glycan species.

Cerebrospinal Fluid Samples

For participants who were randomized in parent study (WN29922 or WN39658) based on CSF Aβ and tau level results who undergo lumbar puncture in the schedule of activities, an aliquot of CSF obtained by lumbar puncture, described in Section 4.5.7.3, will be allocated for the measurement of gantenerumab concentration. Unused sample material may also be used for the purposes of current assay improvement.

4.5.7.2 Plasma Samples for Immunogenicity Analysis

Blood samples will be collected to assess the possible development of ADAs in all participants as noted in the schedule of activities (see Appendix 1). Plasma samples will be analyzed for antibodies to gantenerumab.

Unused sample material may also be used for the purposes of current ADA assay improvement.

4.5.7.3 Biomarker Samples

Samples will be obtained from all participants and will be used for research purposes to identify dynamic biomarkers that may be predictive of response to treatment with gantenerumab (in terms of dose, safety, and tolerability) and will help to better understand the pathogenesis, course, and outcome of AD and related diseases.

For participants who consent to the optional Roche Research Biosample Repository (RBR), residual biomarker samples will be kept for future biomarker research (see Section 4.5.14).

Cerebrospinal Fluid and Serum Biomarkers

CSF samples and matching serum samples will be obtained from participants who were randomized in the parent Study (WN29922 or WN39658) based on CSF Aβ and tau level results. CSF samples will be collected during the study at different timepoints for monitoring the levels of Aβ and tau as well as other CSF biomarkers.

The serum samples collected at every timepoint at which a CSF sample is collected may be used to determine parameters that allow the assessment of blood-brain barrier status and/or inflammatory processes in the brain, such as the CSF/serum albumin ratio, CSF/serum IgG and IgM indices, and oligoclonal bands. CSF and serum samples will be collected according to the schedule of activities (see Appendix 1).

Lumbar puncture will be performed by an individual who meets all local requirements and is proficient in the procedure. Lumbar puncture procedures and post-lumbar puncture care will be performed in accordance with local practice. CSF sampling should be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters. Procedures for processing the CSF samples can be found in the Sample Handling and Logistics Manual.

Approximately 12 mL of CSF will be collected at each timepoint. The sample will be divided into aliquots onsite and used for the following:

- Central measurement of CSF gantenerumab levels
- Analysis of biomarkers in CSF, including $A\beta_{1-42}$, t-tau, p-tau, and other exploratory CSF biomarkers

Samples may also be used to support the development of biomarker assays for diagnostic use.

Plasma Biomarkers

Plasma samples will be collected at different timepoints (see Appendix 1) from every participant who has consented to participate in the study. Samples will be used to evaluate exploratory plasma biomarkers in peripheral blood, which may include, but will not be limited to Aβ, tau, neurofilament, and neurogranin.

An additional plasma sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E).

RNA Biomarkers

Blood samples at different timepoints (see Appendix 1) will be obtained for RNA extraction from every participant who has consented to participate in the study, at OLE Day 1 (only if an RNA sample has not been collected at the final efficacy and safety visit of the parent study [WN29922 or WN39658]), at OLE Week 104 visit, *and OLE Week 208 visit* or OLE early termination visit of this study.

The sample may be used to evaluate clusterin messenger RNA and other exploratory genetic markers in peripheral blood.

Additionally, an RNA blood sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E).

SAMPLING PROCEDURES AND STORAGE

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Roche may keep information about test results, medical history, and demographic information for all participants also from the parent studies for future development of diagnostic tests related to Aβ, *APOE* genotype, and AD, as well as additional analyses.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (Section 4.5.14), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Plasma samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation, therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood, plasma, serum, and CSF samples collected for biomarker research and biomarker assay development will be destroyed no later than 5 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements)

When a participant withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the participant specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.8 Electrocardiograms

Single 12-lead ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

The centrally provided electrocardiograph machine should record the following: heart rate, QRS duration, and RR, PR, and QT intervals and transferred to the Sponsor database from the core laboratory.

At the OLE Day 1 visit or at the visit of the first study drug administration in Study WN42171, ECG does not have to be repeated if the last ECG performed in the parent studies WN29922 or WN39658 occurred within 4 weeks.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the participant has been resting in a supine position for at least 5 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws, brain MRI scans, and lumbar puncture). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site.

4.5.9 Columbia–Suicide Severity Rating Scale

The C-SSRS (http://www.cssrs.columbia.edu) is an assessment tool used to assess the lifetime suicidality of a participant (C-SSRS at baseline) as well as any new instances of suicidality (C-SSRS since last visit). The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual or potential lethality. The C-SSRS baseline from the parent study will be used, and the C-SSRS since the last visit will be collected at subsequent visits as indicated in the schedule of activities (see Appendix 1).

The assessment will be completed by a certified C-SSRS rater after he or she interviews the participant and the participant’s caregiver during the study visit.

4.5.10 Brain Magnetic Resonance Imaging

MRI should be performed using 1.5-T or 3.0-T scanners. Whenever possible, the same scanner should be used for an individual participant for the full duration of the study. The MRI obtained at baseline and/or at the final efficacy and safety visit in the parent study may be used as a baseline measure of structural brain volumes and as baseline information for the PET substudies (see the schedule of activities in Appendix 1).

Where available, exploratory MRI techniques including rs-fMRI and DTI, will also be used.

The MRI from the final efficacy and safety visit of the parent study (WN29922 or WN39658) will be used to determine whether there are any significant findings (e.g., presence of mass lesions, etc.) that may preclude the participant's safe participation in and completion of this study. Similarly, the MRI obtained at the end of the titration in participants who completed the parent study OLE will be used to determine if any significant findings preclude participation in Study WN42171. In case of an ARIA-E finding, the participant should undergo Q4W MRI monitoring until the ARIA-E is resolved. Participants may enroll in study WN42171 once the ARIA-E is resolved using their last MRI in the parent study (WN29922 or WN39658) for eligibility purposes.

MRI will be used during the study to help assess safety, such as the occurrence of ARIA. Additional unscheduled MRI scans may be performed to better understand if relevant CNS adverse events (such as increased confusion) are occurring in the context of ARIA or to follow up a sign that emerges at a scheduled scan; contrast agent may be used in such a case of follow-up MRI scans if administration of contrast agent is considered safe for the participant according to local standards. In addition, structural MRI (to assess whole brain and regional brain atrophy), fMRI, and DTI-MRI will be performed at multiple timepoints to determine potential treatment effects on MRI outcome measures (according to the schedule of activities).

MRI scans will include the following sequences:

- 3D T_1-weighted gradient recalled echo (GRE) scans
- T_2*-weighted GRE scans
- T_2-weighted fluid-attenuated inversion recovery scans
- BOLD rs-fMRI, if available (to assess resting-state functional connectivity at investigative sites having the required software and sequences)
- DTI-MRI, if available (to assess fiber tract integrity)

For details on the specific imaging sequences and acquisition times required, refer to the MRI manual.

Magnetic resonance imaging should not be performed unless at least 3 days have passed since a lumbar puncture. If an MRI and lumbar puncture are both scheduled for the same day, the MRI should be performed first.

MRI scans will be reviewed by a central MRI core laboratory, which will perform the diagnostic reads and assessments of MRI outcome measures. MRI scans should preferably be transferred to the central MRI core laboratory electronically. Data transfer from individual study sites to the central MRI core laboratory may take up to 7−10 days, if not done electronically. Upon receipt of the MRI scans from the study sites, the central MRI core laboratory will provide the diagnostic reads. MRI results must be made available to investigators prior to the dosing visit that the MRI corresponds to (refer to Section 5.1.2 for additional details on MRI safety management).

MRI facility qualification and scan quality control will be performed by the central MRI core laboratory.

In addition to any local reading according to local procedures and requirements, all MRI scans will be reviewed by an expert central reader within approximately 1 week of receipt and a report provided to the site. For the purposes of overall study relevant decisions and recommendations results from the expert central reader will be used. Any time the central reader identifies a new MRI finding, the study center medical staff and the Sponsor will be rapidly notified (see Section 5.1.2).

Refer to Section 5.1.2 for instructions in the event of new MRI findings (ARIA-E and ARIA-H).

At the OLE Day 1 visit or at the visit of the first study drug administration in the Study WN42171, MRI does not have to be repeated if the last MRI performed in the parent studies WN29922 or WN39658 is within 6 months. The MRI can only be used if it was the last prescribed per-protocol MRI in the parent study.

Additional instructions regarding the procedures for MRI scan acquisition and transmittal to the central reading facility can be found in the MRI manual.

Healthy Volunteer Magnetic Resonance Imaging Scans for Site Qualification

In case of a major upgrade to the site's scanner, any other event deemed significant enough to affect image quality, or per central reader guidance, the two volunteers will be asked to complete additional scans that will be reviewed for suitable image quality and used for qualitative comparison. The volunteer must provide written consent to take part in the scanning calibration. Volunteers must not have any contraindications for MRI scanning (evaluation per local procedures at the imaging site), and they will not be enrolled in the study or undergo any other assessments as part of the trial. This procedure will help ensure consistency in scanning quality over the duration of the study. Two volunteers are ideal in case one volunteer is no longer readily available for test scanning.

Additional instructions regarding the procedures for MRI facility qualification can be found in the MRI manual.

4.5.11 Positron Emission Tomography Scan

A PET scan will be performed in the context of the two associated PET substudies (a longitudinal amyloid PET substudy and a longitudinal tau PET substudy (see Section 3.1.2).

Detailed instructions regarding the procedures for PET scan methodology, including scanning procedures, can be found in the PET Technical Operations Manual.

4.5.12 Final Safety and Efficacy Visit Assessments

Participants who complete the treatment period (defined as completion of OLE Week *206* dosing visit) have to complete the final safety and efficacy assessment period 2 weeks following the final dose (Week *208*).

4.5.13 Study Completion or Early Termination Visit Assessments

All participants who withdraw from treatment or discontinue from the study early will be asked to return 2 weeks after the final dose of study drug in order to complete the early termination visit.

In addition, participants who withdraw from treatment will be asked to return for collection of safety (except MRI) and limited efficacy data (i.e., secondary endpoints) at visits that have efficacy assessments (e.g., OLE Week 52, OLE Week 76, OLE Week 104, *OLE Week 130, OLE Week 156, OLE Week 182, OLE Week 208, and OLE Week 220*).

Autopsy reports, including cause of death, for all participants who die during the study (i.e., prior to the OLE Week *220* follow-up visit) should be requested.

Refer to the schedule of activities to be performed at the study completion (OLE Week *208* or OLE early termination visit) in Appendix 1.

When participants complete the treatment period or discontinue early, every effort should be made to ensure that the safety follow-up period and all related assessments are completed.

4.5.14 Optional Samples for Research Biosample Repository

4.5.14.1 Overview of the Research Biosample Repository

The RBR is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for participants in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety

- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.14.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.14) will not be applicable at that site.

4.5.14.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to gantenerumab, AD, or drug safety:

- Leftover blood, serum, plasma, CSF samples collected for biomarker analysis, and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researchers' understanding of disease pathobiology. Whole genome sequencing and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which participants are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.14.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Participant medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.14.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a participant's agreement to provide optional RBR samples. Participants who decline to participate will not provide a separate signature.

The investigator should document whether or not the participant has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.14.6 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the participant. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a participant wishes to withdraw consent to the

testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the participant's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a participant wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and participant number to the following email address:

global.rcr-withdrawal@roche.com

A participant's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a participant's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.14.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to participant participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PARTICIPANT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Participants must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant
- Pregnancy
- Evidence of an intracerebral macrohemorrhage
- Evidence of disseminated leptomeningeal hemosiderosis

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue study treatment prematurely will not be replaced.

All participants who withdraw from treatment will be asked to return 2 weeks after their final dose in order to complete the early termination visit assessments.

In addition, participants who withdraw from treatment will be asked to return for collection of safety data (except MRI) and limited efficacy data (i.e., secondary endpoints) at visits that have efficacy assessments (e.g., OLE Week 52, OLE Week 76, OLE Week 104, *OLE Week 130, OLE Week 156, OLE Week 182, OLE Week 208, and OLE Week 220*) according to the schedule of activities.

4.6.2 Participant Discontinuation from the Study

Participants will return to the clinic for an early termination visit 2 weeks after last dose.

Participants have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a participant from the study at any time.

Reasons for participant discontinuation from the study may include, but are not limited to, the following:

- Participant withdrawal of consent
- Study termination or site closure
- Adverse event or any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues in the study
- Loss to follow-up
- Investigator or Sponsor determines it is in the best interest of the participant
- Participant non-compliance with the study and/or study procedures, defined as missing more than six consecutive dosing visits because of non–safety-related reasons or more than half of the dosing visits in a calendar year

When participants discontinue early, every effort should be made *to ensure that the safety follow-up period and all related assessments are completed and* to obtain a reason for participant discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Participants who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.

- Data from other studies suggest that treatment with gantenerumab is likely not effective.
- Sponsor determines it is the best interest of the participants.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all participants have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Gantenerumab is not yet approved, and clinical development is ongoing. The safety plan for participants in this study is based on clinical experience with gantenerumab in completed and ongoing studies. The identified risks for gantenerumab are outlined below. Please refer to the Gantenerumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of participants participating in this study. Eligibility and discontinuation criteria both in the parent studies (WN29922 and WN39658) and in study WN42171 have been designed to exclude participants at higher risk for imaging-related abnormalities. Participants will undergo safety monitoring during the study, including assessment of the nature, frequency, severity, and timing of adverse events. In addition, guidelines for managing selected adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Gantenerumab

5.1.1.1 Amyloid-Related Imaging Abnormalities

To date, clinical experience with gantenerumab has shown that ARIA events are dose- and APOE ε4-dependent. These events are manageable with MRI monitoring and dose intervention algorithms. In addition, in case of clinical symptoms, the use of IV glucocorticosteroids may be considered.

Rules for management of participants who develop ARIA-E or ARIA-H are provided in Appendix 2.

5.1.1.2 Injection-Site Reactions

Gantenerumab may cause a reaction when given as an SC injection. In studies with gantenerumab, the most common events occurring more frequently with gantenerumab than with placebo were local ISRs, such as injection-site erythema. The majority of events were of mild intensity and resolved without treatment (see Section 1.3.2.2 for details).

Detailed information on the characteristic signs and symptoms of ISRs (e.g., erythema, pruritus) will be recorded on the dedicated eCRF page (see Section 5.3.5.1 for details on recording of ISRs).

5.1.1.3 Immunogenicity

As with administration of any exogenous protein, there is the potential for the development of ADAs, which can be neutralizing and/or sensitizing and which can potentially lead to febrile or allergic reactions, including anaphylaxis. The immunogenic risk of gantenerumab is considered low since it is a fully human antibody.

There are no clinical findings indicative of an immunogenic response to gantenerumab. Investigators should explain to participants how to recognize the signs and symptoms of hypersensitivity reactions, and participants should be monitored.

5.1.2 Management of Participants Who Experience Adverse Events

5.1.2.1 Dose Modifications and Treatment Interruptions

Participants who completed the double-blind part and did not enter the OLE part of the parent Study (WN29922 or WN39658) will undergo uptitration in this study, which will last at least 34 weeks. During the uptitration phase, participants will undergo brain MRI examinations prior to every dose increase (pre-uptitration MRI scans).
The pre-uptitration MRI scans will determine eligibility for the next uptitration dose, as described in Appendix 2.

In order to determine the radiological severity of an ARIA-E event, the Bioclinica 5-point scale (Bracoud et al. 2017) will be used; refer to Table 2.

Table 2 Bioclinica 5-Point Scale Definition

ARIA-E Extent	ARIA-E Focality	5-Point Scale
No ARIA-E	N/A	0
< 5 cm	Monofocal	1 (Mild)
	Multifocal	2 (Mild +)
5–10 cm	Monofocal	3 (Moderate)
	Multifocal	4 (Moderate +)
> 10 cm	Monofocal	5 (Severe)
	Multifocal	

ARIA-E = amyloid-related imaging abnormality–edema/effusion; N/A = not applicable.

The participants' eligibility for uptitration will be determined according to the ARIA management rules outlined in Appendix 2. In the Study WN42171, there must be a minimum of 3 complete administrations of each dosing level for the participants to be eligible for a pre-uptitration MRI scan. A complete IMP administration is defined as two consecutive dosing visits (one with an odd dose number and one with an even dose number (see Appendix 1 and Table 1). A participant may still be eligible for a pre–uptitration MRI scan and uptitration even if these requirements are not met provided that they have been administered IMP at 3 odd dosing visits at a given dose level (see Table 1).

All participants, regardless of where they completed their gantenerumab dose uptitration (i.e., WN22992 or WN39658 OLE or this study), will undergo regular MRI scans according to the schedule of activities while they are on the target gantenerumab dose.

In addition, the dose adjustment and discontinuation rules for MRI findings as described in Appendix 2 will apply.

The investigator may choose to perform additional MRI monitoring for ARIA at any time. MRI monitoring of ARIA findings should be conducted at approximately 4-week intervals. Any other new significant findings will be reviewed by the Medical Monitor, and appropriate dose action will be proposed.

The iDMC will review the incidence of ARIA in an unblinded manner and may recommend adjustment of dosing regimen and/or ARIA management rules for the overall study population or for a specific APOE ε4 genotype. *In the event the iDMC which reviews safety in both the parent studies (WN29922 and WN39658) and study WN42171 is no longer required (for instance after the unblinding of the parent studies) evaluation of participant safety may be taken over by the Sponsor's Internal Monitoring Committee (IMC), with details documented in an IMC charter.*

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.10 and 5.3.5.11 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the participant at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.12)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the participant's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.8).
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.2.4 Selected Adverse Events

Additional data and safety MRI scans will be collected for the following selected adverse events:

- ARIA-E: ARIAs suggestive of vasogenic edema and sulcal effusions

- ARIA-H: ARIAs suggestive of microhemorrhages and/or hemosiderin deposits

Please refer also to Section 5.3.5.2 for further details on how to report ARIA events.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4–5.6.
The investigator is also responsible for reporting medical device complaints (see Section 5.4.4).

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each participant contact.
All adverse events, whether reported by the participant, caregiver, or noted by study personnel, will be recorded in the participant's medical record and on the Adverse Event eCRF.

After informed consent has been obtained:

- All adverse events occurring while the participant is in the parent Study WN29922 or WN39658 will be reported on the parent Adverse Event eCRF until the participant's final visit/last assessment in the parent study.
- All adverse events occurring after the participant's final visit/last assessment in the parent Study WN29922 or WN39658 will be reported on the Study WN42171 Adverse Event eCRF until the participant's final visit/last assessment in Study WN42171 (including long-term follow-up visits).

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all participant evaluation timepoints. Examples of non--directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

Table 3 provides guidance for assessing adverse event severity.

Table 3 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection Reactions

Injection reactions (local and systemic) are defined as adverse events that occur during or within 24 hours after study drug administration that are judged to be related to the study drug injection.

For local reactions, the diagnosis of injection site reaction should be captured on the Adverse Event eCRF and associated signs and symptoms (e.g., erythema at injection site) should be recorded on the dedicated Injection Site Reaction eCRF.

Systemic reactions should be recorded as a single diagnosis on the Adverse Event eCRF (e.g., anaphylactic reaction). If possible, avoid ambiguous terms such as "systemic reaction."

5.3.5.2 ARIA Findings

Not every ARIA finding qualifies as an adverse event. An ARIA finding must be reported as an adverse event if it meets any of the following criteria:

- Symptomatic ARIA-E (onset or worsening of CNS symptom[s] attributable to ARIA-E MRI findings in the judgement of the investigator)
- ARIA findings that result in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Findings that are otherwise clinically significant in the investigator's judgment

Any accompanying symptom(s) should also be captured as separate adverse events. It is the investigator's responsibility to review all ARIA findings. Observations of the same clinically significant ARIA finding should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.3 Diagnosis versus Signs and Symptoms

For adverse events other than ISRs or ARIA (see Sections 5.3.5.1 and 5.3.5.2, respectively), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.4 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.

- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

However, for a serious or severe secondary event such as a fracture following a fall, both events should be reported separately on the eCRF because a fracture is not a typical expected consequence of a fall.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.5 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.6 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN [upper limit of normal] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.7 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.8 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 × ULN) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice in the absence of cholestasis or other

causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ ULN in combination with total bilirubin $>2\times$ ULN
- Treatment-emergent ALT or AST $>3\times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.3) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.9 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of AD.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of AD, "Alzheimer's disease progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.10 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for the parent study and at the beginning of this study. Conditions reported on the General Medical History eCRF in the parent study do not need to be re-entered. They will be reassessed if they are ongoing at the beginning of this study.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept

that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.11 Lack of Efficacy or Worsening of Alzheimer's Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.12 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the *parent study baseline (WN29922 and WN39658)* or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The participant has not experienced an adverse event

5.3.5.13 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug
- In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

Special situations are not in themselves adverse events but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For gantenerumab $and\ [^{18}F]GTP1$, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with gantenerumab $and\ [^{18}F]GTP1$, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.

- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the participant: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries

5.3.5.14 Clinical Outcome Assessment Data

Adverse event reports will not be derived from clinical outcome assessment (COA) data by the Sponsor, and safety analyses will not be performed using COA data. Sites are not expected to review the COA data for adverse events.

5.3.5.15 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2) for details on reporting requirements)

- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2) for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Medical device complaints (see Section 5.4.4 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study participants, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

After informed consent has been obtained:

- All serious adverse events and adverse events of special interest occurring while the participant is in the parent Study (WN29922 or WN39658) will be reported on the parent Adverse Event eCRF until the participant's final visit/last assessment in the parent Study (WN29922 or WN39658).
- All serious adverse events and adverse events of special interest occurring after the participant's final visit/last assessment in the parent Study (WN29922 or WN39658) will be reported on the Study WN42171 Adverse Event eCRF until the participant's final visit/last assessment in Study WN42171 (including long-term follow-up visits).

Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report

via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Participants

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 16 weeks after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female participant exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 Reporting Requirements for Medical Device Complaints

The investigator must report all medical device complaints (e.g., devices for study drug administration) to the Sponsor. The investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the pharmacy manual for further details). If the medical device results in an adverse event to the study participant, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

5.5 FOLLOW-UP OF PARTICIPANTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the participant is lost to follow-up, or the participant withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as participant's final visit/last assessment in Study WN42171) if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Gantenerumab	Gantenerumab Investigator's Brochure
Florbetaben [^{18}F] (Neuraceq™)	Florbetaben [^{18}F] Investigator's Brochure
Flutemetamol [^{18}F] (Vizamyl™)	Flutemetamol [^{18}F] Investigator's Brochure
[^{18}F] GTP1	[^{18}F] GTP1 Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The purpose of this study is to assess the safety, tolerability, and efficacy of long-term administration of open-label gantenerumab in participants with AD who completed Study WN29922 or WN39658.

Data from OLE baseline (see Section 4.5.2 for definition) to the end of study will be summarized. Consequently, where appropriate, data from the parent studies will be combined with data from this protocol.

6.1 DETERMINATION OF SAMPLE SIZE

The sample size will include all eligible participants who consent to this study.
The sample size is expected to be no more than approximately 2032 participants but will be determined by the number of participants who complete parent Studies (WN29922 and WN39658) and enroll in this study.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, participant disposition, and incidence of protocol deviations will be summarized using descriptive statistics for all enrolled participants.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (such as age, sex, race, disease stage, *APOE* ε4 status, and use and non-use of background therapy for AD) will be summarized descriptively for all enrolled participants.

Descriptive summaries of continuous data will present the mean, standard deviation, median, and minimum and maximum. Descriptive summaries of discrete data will include frequencies expressed in terms of number and percentage of participants.

6.4 SAFETY ANALYSES

The safety analysis population will include all enrolled participants who received at least one dose of study drug in this protocol.

The following safety outcome measures will be summarized using descriptive statistics:

- Nature, frequency, severity, timing, and outcomes of adverse events and serious adverse events
- Physical examinations (including neurological systems), vital signs, ECG, laboratory tests, and C-SSRS
- Nature, frequency, severity, and timing of ARIA-E and ARIA-H
- Nature, frequency, severity, timing, and outcomes of injection-site reactions
- Incidence of treatment discontinuations for adverse events
- Incidence of adverse events of special interest

Statistical methods, endpoint definitions, and analyses of the safety endpoints will be described in a SAP.

6.5 EFFICACY ANALYSES

The secondary and exploratory efficacy analyses will use all enrolled participants to investigate both the long-term efficacy and potential disease modifying effect of long-term gantenerumab. Associated estimands, including those pertaining to a delayed start analysis, will be described in detail in a Statistical Analysis Plan (SAP).
The efficacy endpoints collected during both the double-blind and OLE parts of the parent Study (WN29922 or WN39658) may be combined with data from this study in order to evaluate the long-term effect of gantenerumab.

6.6 PHARMACOKINETIC ANALYSES

Plasma concentration data for gantenerumab will be tabulated and summarized. Descriptive summary statistics will include the arithmetic mean, median, range, standard deviation, and coefficient of variation, as appropriate. Because a sparse PK sampling design is being used, population (non-linear mixed-effects) modeling will be used to analyze the dose concentration–time data of gantenerumab. Information from other clinical studies may be incorporated to establish the PK model. The selection of parameters and the derivation of individual measures of exposure, such as area under the concentration–time curve, maximum plasma concentration observed (C_{max}), and trough plasma concentration, will depend on the final PK model used for this analysis. The results of this modeling analysis may be reported separately from the clinical study report. Cerebrospinal fluid concentrations of gantenerumab may be tabulated and summarized as appropriate.

Prior to the completion of the study, one or more separate cutoff date(s) for PK samples may be established to allow expedient sample analyses and early access by third party vendors.

Additional PK analyses will be conducted as appropriate and may be reported separately from the clinical study report.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all participants with at least one ADA assessment. The numbers and proportions of ADA-positive participants and ADA-negative participants prior to OLE drug administration and after OLE drug administration will be summarized using descriptive statistics.

Prior to completion of the study, one or more separate cutoff date(s) for ADA samples may be established to allow expedient samples analyses and early access by third party vendors.

6.8 BIOMARKER ANALYSES

Exploratory PD and biomarker endpoints will be analyzed using descriptive statistics, subgroup analysis, or statistical models if appropriate. For longitudinally measured

endpoints, the change from baseline will be estimated if appropriate. Prior to the completion of the study, one or more separate cutoff date(s) for PD biomarker samples may be established to allow expedient sample analyses and early access by third party vendors. Exploratory biomarkers may be reported separately.

6.9 HEALTH STATUS UTILITY ANALYSES

Change over time in EQ-5D health utility index-based will be calculated. EQ-5D will be summarized using descriptive statistics. Details will be provided in a SAP. EQ-5D will be used to estimate health state utility values needed for economic modeling. Such analyses will be reported separately.

6.10 INTERIM ANALYSES

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one or more interim analysis(es) which may include efficacy, safety and biomarker outcomes. An interim analysis may be considered when the parent pivotal Studies WN29922 and WN39658 are completed and the submission folder is under preparation. Details will be pre-specified in a SAP.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. All electronic data from external vendors will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

COA data will be collected through the use of an electronic device (tablet) provided by a vendor (see Section 7.3 for details). Some COA data may be audio recorded for quality assurance purposes. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR, Part 11).
The electronic data are available for view access only via secure access to an online web portal. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. System

backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

The eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. The eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. The eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive participant data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 ELECTRONIC REPORTED OUTCOME DATA

An electronic device will be used by participants, caregivers, and appropriate site staff to capture COA data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with FDA regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure online web portal. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive participant data for the site in both human- and machine-readable formats that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participant-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated

instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper COA data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each participant the objectives, methods, and potential risks associated with each optional procedure. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a participant's agreement to participate in optional procedures. Participants who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the participant or the participant's legally authorized representative before his or her participation in the study. The case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the participant to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a participant is participating in the study, the participant or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the participant or the participant's legally authorized representative. All signed and dated Consent Forms must remain in each participant's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include participant authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for participant authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the participant, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible

for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each participant enrolled in the study through assignment of a unique patient identification number. This means that participant names are not included in data sets that are transmitted to any Sponsor location.

Participant medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Medical information may be given to a participant's personal physician or other appropriate medical personnel responsible for the participant's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the participant data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring participant safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, participants' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

The overall procedures for quality assurance of clinical study data are described in Roche standard operating procedures. This study will be sponsored by F. Hoffmann-La

Roche Ltd. The Sponsor will provide clinical operations oversight, site monitoring and management, data management support, and medical monitoring.

Study drug distribution may occur through an IxRS (see Section 4.2). Central facilities may be used for study assessments (i.e., ECG, lumbar puncture, specified laboratory tests, PK, rating scales, and MRI and PET imaging), as applicable.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

The results of this study may be published or presented at scientific congresses. For all clinical trials in participants involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in participants involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to participants or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

Table 1 Schedule of Activities for Participants Who Did Not Participate in the OLE Part of Parent Study WN29922 or WN39658

Assessment/Procedure	Screening	BL		OLE (week)																	UV[a]
	Including While in parent study to −1 Day	OLE Day 1	OLE Day 4	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	
Dose number in the Study WN42171		1 [b]		2	3	4	5	6	7	8	9 [c]	10 [c]	11 [c]	12 [c]	13 [d]	14 [c]	15 [c]	16 [c]	17 [c]	18 [c]	
Dose level for participants previously on active		510 mg Q2W																			
Dose level for participants previously on placebo		120 mg							255 mg						510 mg						
Informed consent(s)	x																				
Review of inclusion and exclusion criteria	x	B																			
Medical history, personal status, and demographic data	x																				
Weight and height [e]		x													x						x
Clinical RNA samples		x [b]																			x
Urinalysis		x [r]																			
Coagulation (PT)		B [b]																			
12-Lead ECG		B [b]																			x
Plasma PK sample [f]		B	x												*B*						x
Plasma ADA sample		B													*B*						x

Appendix 1: Schedule of Activities

Assessment/Procedure	Screening	BL		OLE (week)																UV[a]
	Including While in parent study to −1 Day	OLE Day 1	OLE Day 4	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	
Dose number in the Study WN42171		1 [b]		2	3	4	5	6	7	8	9 [c]	10 [c]	11 [c]	12 [c]	13 [d]	14 [c]	15 [c]	16 [c]	17 [c]	18 [c]	
Dose level for participants previously on active		510 mg Q2W																			
Dose level for participants previously on placebo		120 mg							255 mg						510 mg						
Serum chemistry [g] and hematology [h]		B [b]													x						x
Plasma biomarker sample		x [b]													x						x
Complete physical examination (includes neurologic systems) [i]		B[b]																			x
Limited physical examination [j]															x						x
MRI scan [k]		B [b, l]							B						B						x
CSF and matching serum samples [m]		x [b]																			
CDR		P& CG [b]													P& CG						P& CG
ADAS-Cog13		P [b]													P						P
Verbal Fluency Task		P [b]													P						P
Coding		P [b]													P						P

Appendix 1: Schedule of Activities

Assessment/Procedure	Screening	BL		OLE (week)																UV[a]
	Including While in parent study to −1 Day	OLE Day 1	OLE Day 4	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	
Dose number in the Study WN42171		1 [b]		2	3	4	5	6	7	8	9 [c]	10 [c]	11 [c]	12 [c]	13 [d]	14 [c]	15 [c]	16 [c]	17 [c]	18 [c]	
Dose level for participants previously on active		510 mg Q2W																			
Dose level for participants previously on placebo		120 mg							255 mg						510 mg						
ADCS-ADL		CG [b]													CG						CG
FAQ		CG [b]													CG						CG
MMSE		P [b]													P						P
EQ-5D		CG [b]													CG						CG
QoL-AD		P& CG [b]													P& CG						P& CG
ZCI-AD		CG [b]													CG						CG
RUD-Lite		CG [b]													CG						CG
NPI-Q		CG [b]													CG						CG
C-SSRS SLV		P [b]													P						P
Vital signs [n]		B	x	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [o]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [p]		B		B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	

Appendix 1: Schedule of Activities

Assessment/Procedure	Screening	BL		OLE (week)																	UV[a]
	Including While in parent study to −1 Day	OLE Day 1	OLE Day 4	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	
Dose number in the Study WN42171		1 [b]		2	3	4	5	6	7	8	9 [c]	10 [c]	11 [c]	12 [c]	13 [d]	14 [c]	15 [c]	16 [c]	17 [c]	18 [c]	
Dose level for participants previously on active		510 mg Q2W																			
Dose level for participants previously on placebo		120 mg							255 mg						510 mg						
Study drug administration [q]		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

Appendix 1: Schedule of Activities

Aβ = amyloid beta; ADA = anti-drug antibody; ADAS-Cog13 = Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer's Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormality–edema/effusion; ARIA-H = amyloid-related imaging abnormality–microhemorrhage/hemosiderin deposition; BL = baseline; CDR = Clinical Dementia Rating; CSF = cerebrospinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; eCRF=electronic Case Report Form; EQ-5D = EuroQol 5-Dimension Questionnaire; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory Questionnaire; OLE = open-label extension; PK = pharmacokinetic; Q2W = every 2 weeks; QoL–AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SLV = since last visit; T4 = thyroxine; UV = unscheduled visit; ZCI-AD = Zarit Caregiver Interview for Alzheimer's Disease.

B = before study drug administration; CG = caregiver completion; P = participant completion; P&CG = participant and caregiver completion.

Notes: The participant, the site, and the Sponsor will be kept blinded to the dose level given in order to keep the previous treatment assignment blinded. The visit window is ±3 days and +3 days for OLE non-dosing Day 4. It is recommended that not more than 2 dosing visits are given (i.e., 2 × 510 mg Q2W) within 28 days. Participants should return to initial planned schedule per baseline visit (OLE Day 1) for subsequent visits.

[a] The relevant assessments will be determined by the Principal Investigator per clinical judgment, not necessary to include all assessments listed above. An additional plasma and RNA blood sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E); following new or worsened ARIA-E.

[b] Results of standard-of-care tests or examinations (coagulation, ECG, serum chemistry, and hematology; complete physical examination) performed within 4 weeks prior to Day 1 may be used. MRI, C-SSRS, and cognitive scale results may be used if they have been performed *at final efficacy and safety visit of the parent study and* within 6 months prior to OLE Day 1. *MRI must have been performed after the last dose in the parent study.* If a clinical RNA sample or plasma biomarker or CSF and matching serum sample (where applicable) was collected at the final efficacy and safety visit of the parent study, another one does not have to be collected.

[c] At applicable sites, administration of gantenerumab may be performed by a mobile nursing professional at the participant's home or another suitable location, such as a nursing center, to improve access and convenience for participants participating in the study.

[d] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vital signs, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per the schedule of activities, they may be performed up to 4 weeks out of window.

[e] Height will be assessed only at the first dosing visit in Study WN42171.

[f] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following a MRI scan showing new occurrence or worsening of ARIA–E or ARIA-H that meets the discontinuation criteria (e.g., during an unscheduled visit).

[g] Serum chemistry includes AST, ALT, ALP, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). Hemoglobin A_{1c}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after a meal.

[h] Hematology includes WBC count, RBC count (with morphology), hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[i] A complete physical examination, performed at specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated.

[j] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[k] MRI should be performed at least 7 days before dosing, and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[l] Includes resting-state functional MRI and DTI outcome measures, where available.

[m] Lumbar puncture will be performed only in participants who were randomized in Studies WN29922 or WN39658 based on CSF Aβ and tau level results. It must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing (if applicable).

[n] Vital signs include measurements of pulse rate, respiratory rate, systolic and diastolic blood pressure while the participant is in a seated position, and temperature. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[o] After informed consent has been obtained, all adverse events occurring while the participant is in the parent Study WN29922 or WN39658 will be reported on the parent Adverse Event eCRF until the participant's final visit/last assessment in the parent study. After the participant's final visit/last assessment in the parent Study WN29922 or WN39658, all adverse events will be reported on the WN42171 Adverse Event eCRF until the participant's final visit (including long-term follow-up visits).

[p] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[q] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by SC injection (full details are provided in the pharmacy manual). Participants should be observed for at least 2 hours after the first 8 dosing visits. From the ninth dose, this observation time may be reduced to 1 hour. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[r] If deemed necessary by the investigator, urinalysis may be performed at the site by dipstick for blood, protein, glucose, and pH. Microscopic examination will be performed by the central laboratory if blood and/or protein results are positive or strongly positive.

Table 2 Schedule of Activities for Participants Who Have Completed Uptitration in Study WN42171 (continuation of Table 1)

Assessment/Procedure	Treatment Period										Early Term Visit [c]	UV [a]
	OLE (week)											
Study schedule	36	38 [b]	40 [b]	41	42–50 [b]	52 [c]	54–74 [b]	76 [c]	78–102 [b]	103		
Dose number in the Study WN42171	19	20	21		22–26	27	28–38	39	40–52			
Dose level in milligrams (mg)	510 Q2W											
Weight						x		x			x	x
Clinical RNA samples											x	x
12-Lead ECG											x	x
Plasma PK sample [d]				x (Site visit)		B		B		x (Site visit)	x	x
Plasma ADA sample						*B*		B			x	x
Serum chemistry [e] and hematology [f]						x		x			x	x
Plasma biomarker sample						x					x	x
Complete physical examination (includes neurologic systems) [g]											x	x
Limited physical examination [h]	B					B		B				x
MRI scan [i]	B				B W48 [j]			B			x *j*	x

Appendix 1: Schedule of Activities

Assessment/Procedure	Treatment Period										Early Term Visit [c]	UV [a]
	OLE (week)											
Study schedule	36	38 [b]	40 [b]	41	42–50 [b]	52 [c]	54–74 [b]	76 [c]	78–102 [b]	103		
Dose number in the Study WN42171	19	20	21		22–26	27	28–38	39	40–52			
Dose level in milligrams (mg)	510 Q2W											
CSF and matching serum samples [k]						x					x	
CDR						P&CG		P&CG			P&CG	P&CG
ADAS-Cog13						P		P			P	P
Verbal Fluency Task						P		P			P	P
Coding						P		P			P	P
ADCS-ADL						CG		CG			CG	CG
FAQ						CG		CG			CG	CG
MMSE						P		P			P	P
EQ-5D						CG		CG			CG	CG
QoL-AD						P&CG		P&CG			P&CG	P&CG
ZCI-AD						CG		CG			CG	CG
RUD-Lite						CG		CG			CG	CG
NPI-Q						CG		CG			CG	CG

Appendix 1: Schedule of Activities

Assessment/Procedure	Treatment Period										Early Term Visit [c]	UV [a]
	OLE (week)											
Study schedule	36	38 [b]	40 [b]	41	42–50 [b]	52 [c]	54–74 [b]	76 [c]	78–102 [b]	103		
Dose number in the Study WN42171	19	20	21		22–26	27	28–38	39	40–52			
Dose level in milligrams (mg)	510 Q2W											
C-SSRS SLV						P		P			P	P
Vital signs [l]	B	B	B	B	B	B	B	B	B		x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [m]	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [n]	B	B	B		B	B	B	B	B		x	x
Study drug administration [o]	x	x	x		x	x	x	x	x			

Appendix 1: Schedule of Activities

Aβ = amyloid beta; ADA = anti-drug antibody; ADAS-Cog13 = Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer's Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormality–edema/effusion; ARIA-H = amyloid-related imaging abnormality–microhemorrhage/hemosiderin deposition; Assess = assessment; CDR = Clinical Dementia Rating; CSF = cerebrospinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; eCRF = electronic Case report Form; EQ-5D = EuroQol-5 Dimension Questionnaire; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory Questionnaire; OLE = open-label extension; PK = pharmacokinetic; Q2W = every 2 weeks; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; T4 = thyroxine; Term = termination; UV = unscheduled visit; ZCI-AD = Zarit Caregiver Interview for Alzheimer's Disease.

B = before study drug administration; CG = caregiver completion; P = participant completion; P&CG = participant and caregiver completion.

Notes: The visit window is ± 3 days. It is recommended that not more than 2 doses are given (i.e., 2 × 510 mg Q2W) within 28 days. Participants should return to initial planned schedule for subsequent visits.

[a] The relevant assessments will be determined by the Principal Investigator per clinical judgment, not necessary to include all assessments listed above. An additional plasma and RNA blood sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E); following new or worsened ARIA-E.

[b] At applicable sites, administration of gantenerumab may be performed by a mobile nursing professional at the participant's home or another suitable location, such as a nursing center, to improve access and convenience for participants participating in the study.

[c] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vital signs, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per the schedule of activities, they may be performed up to 4 weeks out of window.

[d] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following a MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria (e.g., during an unscheduled visit).

[e] Serum chemistry includes AST, ALT, ALP, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). Hemoglobin A_{1c}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after a meal.

[f] Hematology includes WBC count, RBC count (with morphology), hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[g] A complete physical examination, performed at specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated.

[h] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[i] MRI should be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[j] Includes resting-state functional MRI and DTI outcome measures, where available.

[k] Lumbar puncture will be performed only in participants who were randomized in the WN29922 or WN39658 studies based on CSF Aβ and tau level results. It must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing (if applicable).

[l] Vital signs include measurements of pulse rate, respiratory rate, systolic and diastolic blood pressure while the participant is in a seated position, and temperature. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[m] After informed consent has been obtained, all adverse events occurring while the participant is in the parent Study WN29922 or WN39658 will be reported on the parent Adverse Event eCRF until the participant's final visit/last assessment in the parent study. After the participant's final visit/last assessment in the parent Study WN29922 or WN39658 all adverse events will be reported on the Study WN42171 Adverse Event eCRF until the participant's final visit (including long-term follow-up visits).

[n] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[o] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by SC injection (full details are provided in the pharmacy manual). Participants should be observed for at least 1 hour after dosing. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

Table 3 Schedule of Activities for Participants Who Have Completed the OLE Part of Parent Study WN29922 or WN39658

Assessment/ Procedure	Screening	Treatment Period										Early Term. Visit [c]	UV [a]
		OLE (week)											
Study schedule	Including while in parent study to − 1 day before first dosing visit	36	38 [b]	40 [b]	41	42–50 [b]	52 [c]	54–74 [b]	76 [c]	78–102 [b]	103		
Dose number in the Study WN42171		1	2	3		4–8	9	10–20	21	22–34			
Dose level in milligrams (mg)		510 Q2W											
Informed consent(s)	x												
Review of inclusion and exclusion criteria	x	B [e]											
Medical history, personal status, and demographics	x												
Weight and height [d]		x [e]					x		x			x	x
Clinical RNA samples												x	x
Urinalysis		x [r]											
Coagulation (PT)		B [e]											
12-Lead ECG		B [e]										x	x

Appendix 1: Schedule of Activities

Assessment/ Procedure	Screening	Treatment Period										Early Term. Visit [c]	UV [a]
		OLE (week)											
Study schedule	Including while in parent study to − 1 day before first dosing visit	36	38 [b]	40 [b]	41	42–50 [b]	52 [c]	54–74 [b]	76 [c]	78–102 [b]	103		
Dose number in the Study WN42171		1	2	3		4–8	9	10–20	21	22–34			
Dose level in milligrams (mg)		510 Q2W											
Plasma PK sample [f]		B			x (Site visit)		B		B		x (Site visit)	x	x
Plasma ADA sample		B					B		B			x	x
Serum chemistry [g] and hematology [h]		B [e]					x		x			x	x
Plasma biomarker sample							x					x	x
Complete physical examination (includes neurologic systems) [i]												x	x
Limited physical examination [j]		B [e]					B		B				x
MRI scan [k]		B [e, l]				B W48 [l]			B			x [i]	x

Appendix 1: Schedule of Activities

Assessment/ Procedure	Screening	Treatment Period										Early Term. Visit [c]	UV [a]
		OLE (week)											
Study schedule	Including while in parent study to − 1 day before first dosing visit	36	38 [b]	40 [b]	41	42–50 [b]	52 [c]	54–74 [b]	76 [c]	78–102 [b]	103		
Dose number in the Study WN42171		1	2	3		4–8	9	10–20	21	22–34			
Dose level in milligrams (mg)		510 Q2W											
CSF and matching serum samples [m]							x					x	
CDR		P&CG [e]					P&CG		P&CG			P&CG	P&CG
ADAS-Cog13		P [e]					P		P			P	P
Verbal Fluency Task		P [e]					P		P			P	P
Coding		P [e]					P		P			P	P
ADCS-ADL		CG [e]					CG		CG			CG	CG
FAQ		CG [e]					CG		CG			CG	CG
MMSE		P [e]					P		P			P	P
EQ-5D		CG [e]					CG		CG			CG	CG
QoL-AD		P&CG [e]					P&CG		P&CG			P&CG	P&CG
ZCI-AD		CG [e]					CG		CG			CG	CG

Appendix 1: Schedule of Activities

Assessment/ Procedure	Screening	Treatment Period										Early Term. Visit [c]	UV [a]
		OLE (week)											
Study schedule	Including while in parent study to − 1 day before first dosing visit	36	38 [b]	40 [b]	41	42–50 [b]	52 [c]	54–74 [b]	76 [c]	78–102 [b]	103		
Dose number in the Study WN42171		1	2	3		4–8	9	10–20	21	22–34			
Dose level in milligrams (mg)		510 Q2W											
RUD-Lite		CG [e]					CG		CG			CG	CG
NPI-Q		CG [e]					*CG*		CG			CG	CG
C-SSRS SLV		P [e]					P		P			P	P
Vital signs [n]		B	B	B	B	B	B	B	B	B		x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [o]	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [p]		B	B	B		B	B	B	B	B		x	x
Study drug administration [q]		x	x	x		x	x	x	x	x			

Appendix 1: Schedule of Activities

ADAS-Cog13 = Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormality–edema/effusion; ARIA-H = amyloid-related imaging abnormality–microhemorrhage/hemosiderin deposition; assess = assessment; CDR = Clinical Dementia Rating; CSF = cerebrospinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; eCRF = electronic Case Report Form; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; FU = follow-up; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory Questionnaire; PK = pharmacokinetic; Q2W = every 2 weeks; QoL–AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; term = termination; UV = unscheduled visit; ZCI-AD = Zarit Caregiver Interview for Alzheimer's Disease.

B = before study drug administration; CG = caregiver completion P = participant completion; P&CG = participant and caregiver completion.

Notes: The visit window is ± 3 days and + 3 days for OLE non-dosing Day 4. It is recommended that not more than 2 administrations are given (i.e., 2 × 510 mg Q2W) within 28 days. Participants should return to initial planned schedule per randomization for subsequent visits.

For participants for whom the uptitration in the parent study took longer than 34 weeks to complete, the first visit in Study WN42171 will be adapted according to the schedule of the visits they had in the parent study.

[a] The relevant assessments will be determined by the Principal Investigator per clinical judgment, not necessary to include all assessments listed above. An additional plasma and RNA blood sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E); following new or worsened ARIA-E.

[b] At applicable sites, administration of gantenerumab may be performed by a mobile nursing professional at the participant's home or another suitable location, such as a nursing center, to improve access and convenience for participants participating in the study.

[c] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vital signs, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per schedule of activities they may be performed up to 4 weeks out of window.

[d] Height will be assessed only at the first dosing visit in Study WN42171.

[e] Only for participants who participated in the OLE part of the parent study who are rolling over to this study: Results of standard-of-care tests or examinations (coagulation, ECG, serum chemistry and hematology, complete physical examination) performed in the parent studies within 4 weeks prior to the visit may be used. MRI, C-SSRS, and cognitive scale results may be used if they have been performed within 6 months prior to *the first dosing visit*. MRI must have been performed after the last dose in the parent study.

[f] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following a MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria (e.g., during an unscheduled visit).

[g] Serum chemistry includes AST, ALT, ALP, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). Hemoglobin A_{1c}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after a meal.

[h] Hematology includes WBC count, RBC count (with morphology), hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[i] A complete physical examination, performed at specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated.

[j] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[k] MRI should be performed at least 7 days before dosing, and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[l] Includes resting-state functional MRI and DTI outcome measures, where available.

[m] Lumbar puncture will be performed only in participants who were randomized in Studies WN29922 or WN39658 based on CSF Aβ and tau level results. It must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing (if applicable).

[n] Vital signs include measurements of pulse rate, respiratory rate, systolic and diastolic blood pressure while the participant is in a seated position, and temperature. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[o] After informed consent has been obtained, all adverse events occurring while the participant is in the parent study WN29922 or WN39658 will be reported on the parent Adverse Event eCRF until the participant's final visit/last assessment in the parent study. After the participant's final visit/last assessment in the parent study WN29922 or WN39658 all adverse events will be reported on the Study WN42171 Adverse Event eCRF until the participant's final visit (including long-term follow-up visits).

[p] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[q] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by SC injection (full details are provided in the pharmacy manual). Participants should be observed for at least 1 hour after dosing. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[r] If deemed necessary by the investigator, urinalysis may be performed at the site by dipstick for blood, protein, glucose, and pH. Microscopic examination will be performed by the central laboratory if blood and/or protein results are positive or strongly positive.

Table 4 Schedule of Activities for Participants Who Have Completed Uptitration in Study WN42171 (2-year extension)

Assessment/ Procedure	*Treatment Period*									*Final Safety and Efficacy Assessment*	*Follow-Up Period*	*Early Term. Visit*	*UV [a]*
	OLE (week)												
Study schedule	*104 [c]*	*106–128 [b]*	*130 [c]*	*132–154 [b]*	*156 [c]*	*158—180 [b]*	*182 [c]*	*184—204 [b]*	*206 [b]*	*208 [c]*	*220*		
Dose number in Study WN42171	*53*	*54–65*	*66*	*67–78*	*79*	*80–91*	*92*	*93–103*	*104*				
Dose level in milligrams (mg)	*510 Q2W*												
Weight	*x*		*x*		*x*		*x*			*x*	*x*	*x*	*x*
Clinical RNA samples	*x*									*x*		*x*	*x*
12-lead ECG	*x*										*x*	*x*	*x*
Coagulation (PT)	*B*												
Plasma PK sample [d]					*B*					*x*	*x*	*x*	*x*
Plasma ADA sample	*B*				*B*					*x*	*x*	*x*	*x*
Serum chemistry [e] and hematology [f]	*x*		*x*		*x*		*x*			*x*	*x*	*x*	*x*

Appendix 1: Schedule of Activities

Assessment/ Procedure	Treatment Period									Final Safety and Efficacy Assessment	Follow-Up Period	Early Term. Visit	UV [a]
	OLE (week)												
Study schedule	104 [c]	106–128 [b]	130 [c]	132–154 [b]	156 [c]	158–180 [b]	182 [c]	184–204 [b]	206 [b]	208 [c]	220		
Dose number in Study WN42171	53	54–65	66	67–78	79	80–91	92	93–103	104				
Dose level in milligrams (mg)	510 Q2W												
Plasma biomarker sample	x				x					x		x	x
Complete physical examination (includes neurologic systems) [g]	B									x		x	x
Limited physical examination [h]			B		B		B						x
MRI scan [i]	B [j]		B		B [j]		B			x [j]		x [j]	x
CSF and matching serum samples [k]	x				x					x		x	
CDR	P&CG		P&CG		P&CG		P&CG			P&CG		P&CG	P&CG
ADAS-Cog13	P		P		P		P			P		P	P
Verbal Fluency Task	P		P		P		P			P		P	P

Appendix 1: Schedule of Activities

Assessment/ Procedure	*Treatment Period*									*Final Safety and Efficacy Assessment*	*Follow-Up Period*	*Early Term. Visit*	*UV* [a]
	OLE (week)												
Study schedule	*104* [c]	*106–128* [b]	*130* [c]	*132–154* [b]	*156* [c]	*158—180* [b]	*182* [c]	*184—204* [b]	*206* [b]	*208* [c]	*220*		
Dose number in Study WN42171	*53*	*54–65*	*66*	*67–78*	*79*	*80–91*	*92*	*93–103*	*104*				
Dose level in milligrams (mg)	*510 Q2W*												
Coding	*P*		*P*		*P*		*P*			*P*		*P*	*P*
ADCS-ADL	*CG*		*CG*		*CG*		*CG*			*CG*		*CG*	*CG*
FAQ	*CG*		*CG*		*CG*		*CG*			*CG*		*CG*	*CG*
MMSE	*P*		*P*		*P*		*P*			*P*		*P*	*P*
EQ-5D	*CG*				*CG*					*CG*		*CG*	*CG*
QoL-AD	*P&CG*				*P&CG*					*P&CG*		*P&CG*	*P&CG*
ZCI-AD	*CG*				*CG*					*CG*		*CG*	*CG*
RUD-Lite	*CG*				*CG*					*CG*		*CG*	*CG*
NPI-Q	*CG*				*CG*					*CG*		*CG*	*CG*
C-SSRS SLV	*P*		*P*		*P*		*P*			*P*		*P*	*P*
Vital signs [l]	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*x*	*x*	*x*	*x*
Concomitant medications	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Adverse events [m]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*

Appendix 1: Schedule of Activities

Assessment/ Procedure	Treatment Period									Final Safety and Efficacy Assessment	Follow-Up Period	Early Term. Visit	UV [a]
	OLE (week)												
Study schedule	104 [c]	106–128 [b]	130 [c]	132–154 [b]	156 [c]	158–180 [b]	182 [c]	184–204 [b]	206 [b]	208 [c]	220		
Dose number in Study WN42171	53	54–65	66	67–78	79	80–91	92	93–103	104				
Dose level in milligrams (mg)	510 Q2W												
Urine pregnancy test [n]	B	B	B	B	B	B	B	B	B	x	x	x	x
Study drug administration [o]	x	x	x	x	x	x	x	x	x				

Aβ =amyloid beta; ADA =anti-drug antibody; ADAS-Cog13 =Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL =Alzheimer's Disease Cooperative Study Group–Activities of Daily Living; ARIA-E =amyloid-related imaging abnormality–edema/effusion; ARIA-H =amyloid-related imaging abnormality–microhemorrhage/hemosiderin deposition; Assess =assessment; B =before study drug administration; CDR =Clinical Dementia Rating; CG =caregiver completion; CSF =cerebrospinal fluid; C-SSRS =Columbia–Suicide Severity Rating Scale; DTI =diffusion tensor imaging; eCRF =electronic Case report Form; EQ-5D =EuroQol-5 Dimension Questionnaire; FAQ =Functional Activities Questionnaire; MMSE =Mini-Mental State Examination; MRI =magnetic resonance imaging; NPI-Q =Neuropsychiatric Inventory Questionnaire; OLE =open-label extension; P&CG =participant and caregiver completion; P =participant completion; PK =pharmacokinetic; Q2W =every 2 weeks; QoL-AD =Quality of Life–Alzheimer's Disease; RUD-Lite =Resource Utilization in Dementia–Lite; T4 =thyroxine; Term =termination; UV =unscheduled visit; ZCI-AD =Zarit Caregiver Interview for Alzheimer's Disease.

Notes: The visit window is ±3 days. It is recommended that not more than 2 doses are given (i.e., 2 ×510 mg Q2W) within 28 days. Participants should return to initial planned schedule per randomization for subsequent visits.

[a] *The relevant assessments will be determined by the Principal Investigator per clinical judgment, not necessary to include all assessments listed above. An additional plasma and RNA blood sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E); following new or worsened ARIA-E.*

[b] *At applicable sites, administration of gantenerumab may be performed by a mobile nursing professional at the participant's home or another suitable location, such as a nursing center, to improve access and convenience for participants participating in the study.*

[c] *Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vital signs, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per the schedule of activities, they may be performed up to 4 weeks out of window.*

[d] *Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following a MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria (e.g., during an unscheduled visit).*

[e] *Serum chemistry includes AST, ALT, ALP, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). Hemoglobin A1c, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after a meal.*

[f] *Hematology includes WBC count, RBC count (with morphology), hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).*

[g] *A complete physical examination, performed at specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated.*

[h] *Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.*

[i] *MRI should be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.*

[j] *Includes resting-state functional MRI and DTI outcome measures, where available.*

[k] *Lumbar puncture will be performed only in participants who were randomized in the WN29922 or WN39658 studies based on CSF Aβ and tau level results. It must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing (if applicable).*

[l] *Vital signs include measurements of pulse rate, respiratory rate, systolic and diastolic blood pressure while the participant is in a seated position, and temperature. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.*

[m] *After informed consent has been obtained, all adverse events occurring while the participant is in the parent Study WN29922 or WN39658 will be reported on the parent Adverse Event eCRF until the participant's final visit/last assessment in the parent study. After the participant's final visit/last assessment in the parent Study WN29922 or WN39658 all adverse events will be reported on the Study WN42171 Adverse Event eCRF until the participant's final visit (including long-term follow-up visits).*

[n] *Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.*

[o] *Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by SC injection (full details are provided in the pharmacy manual). Participants should be observed for at least 1 hour after dosing. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.*

Table 5 Schedule of Activities for Participants Who Have Completed the OLE Part of Parent Study WN29922 or WN39658 (2-Year Extension)

Assessment/ Procedure	Treatment Period									Final Safety and Efficacy Assessment	Follow-Up Period	Early Term. Visit	UV [a]
	OLE (week)												
Study schedule	104 [c]	106–128 [b]	130 [c]	132–154 [b]	156 [c]	158—180 [b]	182 [c]	184—204 [b]	206 [b]	208 [c]	220		
Dose number in Study WN42171	35	36–47	48	49–60	61	62–73	74	75–85	86				
Dose level in milligrams (mg)	510 Q2W												
Weight	x		x		x		x			x	x	x	x
Clinical RNA samples	x									x		x	x
12-lead ECG	x										x	x	x
Coagulation (PT)	B												
Plasma PK sample [d]					B					x	x	x	x
Plasma ADA sample	B				B					x	x	x	x
Serum chemistry [e] and hematology [f]	x		x		x		x			x	x	x	x

Appendix 1: Schedule of Activities

Assessment/ Procedure	Treatment Period									Final Safety and Efficacy Assessment	Follow-Up Period	Early Term. Visit	UV [a]
	OLE (week)												
Study schedule	104 [c]	106–128 [b]	130 [c]	132–154 [b]	156 [c]	158–180 [b]	182 [c]	184–204 [b]	206 [b]	208 [c]	220		
Dose number in Study WN42171	35	36–47	48	49–60	61	62–73	74	75–85	86				
Dose level in milligrams (mg)	510 Q2W												
Plasma biomarker sample	x				x					x		x	x
Complete physical examination (includes neurologic systems) [g]	B									x		x	x
Limited physical examination [h]			B		B		B						x
MRI scan [i]	B [j]		B		B [j]		B			x [j]		x [j]	x
CSF and matching serum samples [k]	x				x					x		x	
CDR	P&CG		P&CG		P&CG		P&CG			P&CG		P&CG	P&CG
ADAS-Cog13	P		P		P		P			P		P	P

Appendix 1: Schedule of Activities

Assessment/ Procedure	*Treatment Period*									*Final Safety and Efficacy Assessment*	*Follow-Up Period*	*Early Term. Visit*	*UV* [a]
	OLE (week)												
Study schedule	*104* [c]	*106–128* [b]	*130* [c]	*132–154* [b]	*156* [c]	*158—180* [b]	*182* [c]	*184—204* [b]	*206* [b]	*208* [c]	*220*		
Dose number in Study WN42171	*35*	*36–47*	*48*	*49–60*	*61*	*62–73*	*74*	*75–85*	*86*				
Dose level in milligrams (mg)	*510 Q2W*												
Verbal Fluency Task	*P*		*P*		*P*		*P*			*P*		*P*	*P*
Coding	*P*		*P*		*P*		*P*			*P*		*P*	*P*
ADCS-ADL	*CG*		*CG*		*CG*		*CG*			*CG*		*CG*	*CG*
FAQ	*CG*		*CG*		*CG*		*CG*			*CG*		*CG*	*CG*
MMSE	*P*		*P*		*P*		*P*			*P*		*P*	*P*
EQ-5D	*CG*				*CG*					*CG*		*CG*	*CG*
QoL-AD	*P&CG*				*P&CG*					*P&CG*		*P&CG*	*P&CG*
ZCI-AD	*CG*				*CG*					*CG*		*CG*	*CG*
RUD-Lite	*CG*				*CG*					*CG*		*CG*	*CG*
NPI-Q	*CG*				*CG*					*CG*		*CG*	*CG*
C-SSRS SLV	*P*		*P*		*P*		*P*			*P*		*P*	*P*
Vital signs [1]	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*x*	*x*	*x*	*x*

Appendix 1: Schedule of Activities

Assessment/ Procedure	Treatment Period									Final Safety and Efficacy Assessment	Follow-Up Period	Early Term. Visit	UV [a]
	OLE (week)												
Study schedule	104 [c]	106–128 [b]	130 [c]	132–154 [b]	156 [c]	158–180 [b]	182 [c]	184–204 [b]	206 [b]	208 [c]	220		
Dose number in Study WN42171	35	36–47	48	49–60	61	62–73	74	75–85	86				
Dose level in milligrams (mg)	510 Q2W												
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [m]	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [n]	B	B	B	B	B	B	B	B	B	x	x	x	x
Study drug administration [o]	x	x	x	x	x	x	x	x	x				

Aβ =amyloid beta; ADA =anti-drug antibody; ADAS-Cog13 =Alzheimer's Disease Assessment Scale−Cognition, Subscale 13; ADCS-ADL =Alzheimer's Disease Cooperative Study Group−Activities of Daily Living; ARIA-E =amyloid-related imaging abnormality−edema/effusion; ARIA-H =amyloid-related imaging abnormality−microhemorrhage/hemosiderin deposition; Assess =assessment; B =before study drug administration; CDR =Clinical Dementia Rating; CG =caregiver completion; CSF =cerebrospinal fluid; C-SSRS =Columbia−Suicide Severity Rating Scale; DTI =diffusion tensor imaging; eCRF =electronic Case report Form; EQ-5D =EuroQol-5 Dimension Questionnaire; FAQ =Functional Activities Questionnaire; MMSE =Mini-Mental State Examination; MRI =magnetic resonance imaging; NPI-Q =Neuropsychiatric Inventory Questionnaire; OLE =open-label extension; P&CG =participant and caregiver completion; P =participant completion; PK =pharmacokinetic; Q2W =every 2 weeks; QoL-AD =Quality of Life−Alzheimer's Disease; RUD-Lite =Resource Utilization in Dementia−Lite; T4 =thyroxine; Term =termination; UV =unscheduled visit; ZCI-AD =Zarit Caregiver Interview for Alzheimer's Disease.

Notes: The visit window is ±3 days. It is recommended that not more than 2 doses are given (i.e., 2 ×510 mg Q2W) within 28 days. Participants should return to initial planned schedule per randomization for subsequent visits.

[a] *The relevant assessments will be determined by the Principal Investigator per clinical judgment, not necessary to include all assessments listed above. An additional plasma and RNA blood sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E); following new or worsened ARIA-E.*

[b] *At applicable sites, administration of gantenerumab may be performed by a mobile nursing professional at the participant's home or another suitable location, such as a nursing center, to improve access and convenience for participants participating in the study.*

[c] *Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vital signs, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per the schedule of activities, they may be performed up to 4 weeks out of window.*

[d] *Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following a MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria (e.g., during an unscheduled visit).*

[e] *Serum chemistry includes AST, ALT, ALP, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). Hemoglobin A1c, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after a meal.*

[f] *Hematology includes WBC count, RBC count (with morphology), hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).*

[g] *A complete physical examination, performed at specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated.*

[h] *Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.*

[i] *MRI should be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.*

[j] *Includes resting-state functional MRI and DTI outcome measures, where available.*

[k] *Lumbar puncture will be performed only in participants who were randomized in the WN29922 or WN39658 studies based on CSF Aβ and tau level results. It must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing (if applicable).*

[l] *Vital signs include measurements of pulse rate, respiratory rate, systolic and diastolic blood pressure while the participant is in a seated position, and temperature. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.*

[m] *After informed consent has been obtained, all adverse events occurring while the participant is in the parent Study WN29922 or WN39658 will be reported on the parent Adverse Event eCRF until the participant's final visit/last assessment in the parent study. After the participant's final visit/last assessment in the parent Study WN29922 or WN39658 all adverse events will be reported on the Study WN42171 Adverse Event eCRF until the participant's final visit (including long-term follow-up visits).*

[n] *Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.*

[o] *Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise. Study drug will be administered to participants by SC injection (full details are provided in the pharmacy manual). Participants should be observed for at least 1 hour after dosing. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.*

Appendix 2 Management Rules for Amyloid-Related Imaging Abnormalities

Event	Characteristic	Action to Be Taken
ARIA-E	Asymptomatic and mild (Bioclinica severity 1)	• Continue study drug according to the schedule of administration (including uptitration). • Perform MRI scans at 4-week intervals until ARIA-E resolves. • Then, resume the standard MRI schedule.
	Asymptomatic and mild+ (Bioclinica severity 2) or moderate (Bioclinica severity 3)	**During uptitration period:** • Continue study drug at the same dose level and do not uptitrate. • Perform MRI scans at 4-week intervals until ARIA-E resolves. • Once ARIA-E resolves, continue uptitration and resume the standard MRI schedule. **During treatment period (at target dose):** • Continue study drug according to the schedule of administration. • Perform MRI scans at 4-week intervals until ARIA-E resolves. Then, resume the standard MRI schedule.
	Asymptomatic and moderate+ (Bioclinica severity 4) or severe (Bioclinica severity 5) Or Symptomatic ARIA-E [a] of any severity (Bioclinica severity 1–5)	**During uptitration period:** • Temporarily interrupt study drug. • Perform MRI scans at 4-week intervals until ARIA-E (and any ARIA-E symptom/s) resolves. • Once ARIA-E (and any ARIA-E symptom/s) resolves, reintroduce study drug at the dose level given at the time the event was detected. • Perform an MRI scan after two consecutive dosing visits. • If no new ARIA-E is detected, continue uptitration and resume the standard MRI schedule. **During treatment period (at target dose):** • Temporarily interrupt study drug. • Perform MRI scans at 4-week intervals until ARIA-E (and any ARIA-E symptom/s) resolves. • Once ARIA-E (and any ARIA-E symptom/s) resolves, reintroduce study drug. • Perform an MRI scan after two consecutive dosing visits. • If no new ARIA-E is detected, resume the standard MRI schedule.
	Any recurrence of ARIA-E	• Treat as above.

Appendix 2: Management Rules for Amyloid-Related Imaging Abnormalities

Event	Characteristic	Action to Be Taken
ARIA-H	Without disseminated LH	• Continue study drug according to the schedule of administration (including uptitration). • Perform MRI scans according to the standard MRI schedule.
	Disseminated LH	• Permanently discontinue study drug.

ARIA-E = amyloid-related imaging abnormality–edema/effusion; ARIA-H = amyloid-related imaging abnormality–microhemorrhage/hemosiderin deposition; LH = leptomeningeal hemosiderosis; MRI = magnetic resonance imaging; PK = pharmacokinetic; Q4W = every 4 weeks.

Notes:

- Disseminated LH is defined as more than three focal leptomeningeal hemosiderosis cumulatively.
- If ARIA-E and disseminated LH co-occur, the more conservative management rule will apply.
- The investigator may choose to perform additional MRI monitoring for ARIA at any time.
- In exceptional cases of 1) an ARIA-E that is asymptomatic with Bioclinica severity 1 and considered stable over consecutive MRI images by the Sponsor and investigator; or 2) symptomatic ARIA-E for which the imaging evidence of ARIA-E has resolved but the CNS symptoms continue, gantenerumab can be either reintroduced or uptitrated, as applicable, and Q4W MRI monitoring may no longer be necessary, as determined by the Sponsor and investigator.
- A PK sample will be obtained as soon as soon as practicable (e.g., at an unscheduled visit or the next study visit) following a MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria (e.g., during an unscheduled visit).
- An additional plasma and RNA sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E).

[a] Symptomatic ARIA-E is defined as onset or worsening of CNS symptom(s) that is/are attributable to ARIA-E MRI findings in the judgement of the Principal Investigator or appropriately medically qualified subinvestigator.

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Protocol - WN42171 - GANTENERUMAB (MAIN) - v4 - Global/Core - Published

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PostGraduate (PROTOCOL WN42171)

SUMMARY OF CHANGES

AN OPEN-LABEL, MULTICENTER, ROLLOVER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF LONG-TERM GANTENERUMAB ADMINISTRATION IN PARTICIPANTS WITH ALZHEIMER'S DISEASE

PROTOCOL AMENDMENT, VERSION 2: RATIONALE

Protocol WN42171 has been amended with changes, as summarized below, along with a rationale for each change given:

- Descriptions of the Marguerite RoAD open-label extension (OLE) study cohorts in the amyloid positron emission tomography (PET) substudy have been updated in Section 1.3.1 and in the Figure 1 legend to align with the abbreviations used in Figure 1
- Assessment of the impact of the Coronavirus Disease-2019 (COVID-19) pandemic on Study WN42171 and an assessment of concomitant administration of the COVID-19 vaccine with gantenerumab as per Medicines and Healthcare Products Regulatory Agency (MHRA) requirements has been included in Section 1.3.2.3.
- Section 2.3 has been updated to reflect that the pharmacokinetic (PK) objectives of the Study WN42171 are exploratory, consistent with the sparse PK sampling design and population modeling used to analyze the dose concentration-time data of gantenerumab, and consistent with its exploratory status in the parent Studies WN29922 and WN3965. Early access will only be applied if there are sufficient sample data available to make an adequate assessment.
- Section 2.5 has been updated to clarify that the biomarker objectives of this study are exploratory, consistent with the open-label extension nature of the study.
- Section 3.1.1 has been updated to clarify that participants may roll over from the safety follow-up of the parent Study (WN29922 or WN39658), in the event that participants temporarily meet exclusion criteria for the study, for e.g., due to ongoing amyloid-related imaging abnormality-edema/effusion (ARIA-E) at the end of the parent study double-blind period.
- Language has been included in Section 3.1.3. to clarify that in the event the independent Data Monitoring Committee (iDMC), which reviews safety in both the parent Studies (WN29922 and WN39658) and Study WN42171, is no longer required (for instance after the unblinding of the parent studies), evaluation of participant safety will be taken over by the Sponsor’s Internal Monitoring Committee (IMC), with details documented in an IMC charter.
- Sections 3.1.1, 4.4.1, 4.5.1, and 5.1.2.1 have been revised to clarify the Medical Monitor’s responsibility to review and support patient cohort management and other protocol activities. Any reference to approval by the Medical Monitor with regards to medical decisions following enrollment has been removed from the protocol. This means that the Principal Investigator (PI) may consult with the Medical Monitor/Sponsor for advice or clarification and may share risk factor information pertinent to the participant, but the medical decisions for the study participants are the responsibility of the PI.

- Section 4.1.1 (Inclusion Criteria) have been updated to:
  - Clarify that ability to complete lumbar puncture is not a requirement for inclusion in the study, because it is not a key safety assessment, unlike magnetic resonance imaging.
  - Include the requirement for a caregiver during the study, which is consistent with the parent Studies (WN29922 and WN39658) and a requirement for the completion of important secondary efficacy endpoints, such as the Clinical Dementia Rating (CDR).
  - Include the requirement to agree not to donate blood or blood products during the study and for one year after final dose, consistent with the parent Studies (WN29922 and WN39658) and other studies assessing investigational monoclonal antibodies
- Language has been added to clarify the minimum number of dosing visits required to be eligible for uptitration, to avoid unnecessary delays in uptitration (Section 4.3.2).
- Section 4.4.1 has been updated to reflect less stringent requirements regarding permitted medication that do not have an impact on participant safety.
- Language has been added to reflect that approved passive immunotherapy, designed to prevent or postpone cognitive decline, is also prohibited, to ensure participants do not receive other drugs with the same mechanism of action (Section 4.4.2).
- Language has been added to clarify that preferably the same assessor performs the CDR in both the parent Study (WN29922 or WN39658) and Study WN42171, to facilitate long-term efficacy analyses (Section 4.5.6.1)
- Section 4.5.6.8. has been updated to reflect that in case a participant's study partner changes, collection of data using the Zarit Caregiver Interview Alzheimer's Disease (ZCI) scale will continue (rather than stop) in order to minimize missing data.
- Language has been added to reflect that an RNA biomarker sample will not be collected at the first visit for those that rolled over from the parent Study (WN29922 or WN39658) OLE, as the number of samples at this time point will be small with limited scientific value (Section 4.5.7.3).
- Language has been added to clarify the timing of onset of adverse event (AE) reporting in Study WN42171, which was previously inconsistently described between sections (Section 5.3.1; 5.4.2; and Appendix 1).
- Language has been added to indicate that instructions for safety reporting of injection reactions are consistent between Study WN42171 and the parent Studies WN29922 and WN39658 to facilitate long-term safety analyses (Section 5.3.5.1).
- Language has been added to clarify that AEs associated with a special situation that also qualify as adverse events of special interest should be reported within 24 hours (Section 5.3.5.13).
- Emergency Medical Contacts has been updated in line with changes in study personnel (Section 5.4.1)
- Language has been added to clarify that separate data delivery cut off date(s) may be necessary for pharmacodynamic (PD) biomarker, pharmacokinetic, and anti-drug antibody (ADA) samples to allow early access to PD biomarker samples and ensure expedient data analyses (Sections 6.6, 6.7, and 6.8).
- Language has been added to include additional details surrounding the conduct of an interim analysis, should one be implemented (Section 6.10).

- The name of a Roche policy on data sharing has been corrected (Section 9.6).
- Appendix 1 (Schedule of Activities; Tables 1 and 2) have been updated to correct minor errors and inconsistencies which were previously clarified in Notes to File, and to extend the number of visits available for home nursing administration when at target dose, to increase flexibility for participants. The ADA sample at Week 103 has been replaced with a Week 76 sample, since Week 103 is a C_{max} sample with high gantenerumab concentrations making it unlikely to detect ADAs.
- References to Week 104 of the parent study have been updated to "final efficacy and safety visit" to reflect that in PA4 of the parent Studies WN29922/WN39658 and subsequent amendments the final efficacy and safety visit was extended from Week 104 to Week 116 in response to the COVID-19 pandemic.

Additional minor changes have been made to improve clarity and consistency.
Substantive new information appears in *italics*. This amendment represents cumulative changes to the original protocol.

AN OPEN-LABEL, MULTICENTER, ROLLOVER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF LONG-TERM GANTENERUMAB ADMINISTRATION IN PARTICIPANTS WITH ALZHEIMER'S DISEASE

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol WN42171 has been amended primarily to extend the open-label treatment (OLE) period from 2 to 4 years. The changes to the protocol, along with a rationale for each change, are summarized below. Note that as Version 3 of the protocol was either withdrawn or not submitted, Version 4 will reflect all changes from Version 2 in italics.

- Section 1.3.1 has been updated to reflect that with the 2-year extension participants will receive open-label gantenerumab for up to 4 years.
- Sections 1.2.1 and 1.3.2.3 have been updated to reflect that Studies WN25203 and WN28745 are completed.
- Section 1.3.2.3 has been updated to clarify that no interactions between positron emission tomography (PET) tracers and the coronavirus disease 2019 (COVID-19) vaccines are expected to occur based on the available information.
- The secondary efficacy objective included change over time in cognition and/or function. The reference to “change over time of other outcomes” has been removed since the other outcomes are exploratory efficacy endpoints.
- Section 3.1.1 has been updated to include that the participants will be treated for 4 years with the last visit in the study at OLE-Week 208 and the follow-up visit at OLE-Week 220. The study period extension will allow the collection of more information on the long-term safety and tolerability of gantenerumab in Alzheimer’s Disease (AD) and its efficacy in the context of long-term exposure, thus increasing understanding of gantenerumab’s long term safety and efficacy profile. In addition, it will allow to better understand the long-term effect of gantenerumab on the pathophysiology of AD as well as changes on Study biomarkers.
- Section 3.2 has been updated to reflect that with the 2-year extension, the total duration of the study from baseline visit is expected to be approximately 4 years with the end of the study expected to occur by the end of 2026.
- Section 3.3.3.2 has been added to include the rationale for the additional 2 years. The extension of the study treatment duration from 2 to 4 years will allow the collection of more longitudinal safety and efficacy information of gantenerumab in AD.
- Sections 4.4.1 and 4.4.2 have been updated to reflect less stringent requirements regarding permitted medication that do not have an impact on participant safety and to clarify that study drug should be temporarily interrupted whilst anticoagulation therapy is ongoing.
- Section 4.4.1 has been updated to clarify that the administration of COVID-19 vaccines will be considered, just as with other vaccinations, as a concomitant medication and that it is recommended to avoid vaccination in the 48 hours around the study dug injection to facilitate the correct attribution of adverse events (AEs).
- Section 4.5.3 has been amended to clarify that collecting ethnicity data facilitates evaluation of whether gantenerumab is metabolized or eliminated differently or if the treatment effect will be different in participants of different ethnic origins.
- Sections 4.5.4, 4.5.6.1, 4.5.7.3, 4.5.12, 4.5.13, 4.6.1 and Appendix 1 have been amended to reflect that OLE-W104 is a dosing visit and not the final efficacy and

safety visit, to include additional visits during the study extension with the last visit in the study at OLE-Week 208 and to reflect that the follow-up visit will be at OLE-Week 220 and not at OLE-W116.

- Section 4.5.6.13 has been updated to reflect that the Zarit Caregiver Interview for Alzheimer's Disease (ZCI-AD) scale is also captured electronically. This was omitted in error.
- Section 5.3.5.4 has been amended to clarify reporting of serious or severe secondary events.
- The reporting of adverse events and serious adverse events related to preexisting conditions prior to the parent study baseline has been clarified to ensure the correct collection of data in view of the combined analysis with the data from the parent studies (Sections 5.3.5.12 and 5.3.5.13).
- The Medical Monitor and applicable contact information have been aligned throughout the protocol and deleted from Section 5.4.1. To avoid the inclusion of outdated phone numbers in the protocol, the protocol refers to the Emergency Medical Call Center Help Desk, which will always have an up-to-date list of Medical Monitor and Medical Responsible contact information.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

STATISTICAL ANALYSIS PLAN

STUDY TITLE:	**AN OPEN-LABEL, MULTICENTER, ROLLOVER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF LONG-TERM GANTENERUMAB ADMINISTRATION IN PARTICIPANTS WITH ALZHEIMER'S DISEASE**
STUDY NUMBER:	WN42171
STUDY NAME:	POSTGRADUATE
VERSION NUMBER:	1.0
ROCHE COMPOUND(S):	Gantenerumab (RO4909832)
EUDRACT NUMBER:	2020-000766-42
IND NUMBER:	102,266
NCT NUMBER:	NCT04374253
PLAN PREPARED BY:	[redacted] Ph.D., [redacted] M.Sc., [redacted] Ph.D.

STATISTICAL ANALYSIS PLAN APPROVAL

SPONSOR:	F. Hoffmann-La Roche Ltd
LEGAL REGISTERED ADDRESS:	Grenzacherstrasse 124 4070 Basel, Switzerland
DATE FINAL:	See electronic date stamp on the last page of this document

STATISTICAL ANALYSIS PLAN VERSION HISTORY

This SAP was developed based on Roche SAP model document v2.0, revised 26 October 2020.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	see electronic date stamp on the last page of this document	Version 4.0, 11 May, 2022

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
[^{18}F]GTP1	Genentech Tau Probe 1
AD	Alzheimer's Disease
ADA	anti-drug antibody
ADAS-Cog	Alzheimer Disease Assessment Scale-Cognition
ADCS-ADL	Alzheimer Disease Cooperative Study Group-Activities of Daily Living
AE	adverse event
ARIA-E	amyloid-related imaging abnormalities – edema/effusion
ARIA-H	amyloid-related imaging abnormalities – hemosiderin deposition
BGTS	Barkhof Grand Total Score
CDR	Clinical Dementia Rating
CSR	Clinical Study Report
C-SSRS	Columbia-suicide severity rating scale
DSST	Digit Symbol Substitution Test
EQ-5D	EuroQol 5-Dimension Questionnaire
FAQ	Functional Activities Questionnaire
iDMC	independent Data Monitoring Committee
IMC	Internal Monitoring Committee
ISR	injection site reaction
ITT	intent to treat
IxRS	interactive voice/web-based response system
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NMPA	National Medical Products Administration
NPI-Q	Neuropsychiatric Inventory Questionnaire
OLE	open-label extension
PET	positron emission tomography
PD	Pharmacodynamic
PK	Pharmacokinetic
Q2W	Every two weeks
QoL-AD	Quality of Life-Alzheimer's Disease
RUD-Lite	Resource Utilization in Dementia-Lite
SAE	serious adverse events
SAP	Statistical Analysis Plan
SC	Subcutaneous
SUVR	standard uptake value ratio

ZCI-AD Zarit Caregiver Interview for Alzheimer's Disease

1. INTRODUCTION

This document describes the statistical analyses that will be reported in the Clinical Study Report (CSR) of Study WN42171 (hereafter referred to as "POSTGRADUATE"). This document will focus on the statistical methodology underlying the report that will include participant disposition, baseline demographics, descriptive efficacy and standard safety outputs along with the analysis sets.

This Statistical Analysis Plan (SAP) covers analyses planned for POSTGRADUATE study only. Analyses planned across the double-blind period in the pivotal parent studies WN29922 and WN39658 (hereafter referred to as "GRADUATE I" and "GRADUATE II", respectively), the open-label extension (OLE) period in the GRADUATE studies and POSTGRADUATE are described separately and not the subject of this SAP.

Analyses planned for the longitudinal amyloid positron emission tomography (PET) and tau-PET substudies are provided in Sections 5.7.6 and 5.7.7. The pharmacokinetic (PK) data and PK/PD modelling will be reported in the population PK report and are therefore not covered in this document. Similarly, health economic data (such as utility values derived from the EuroQoL–5 Dimensions [EQ-5D] and the Resource Utilization in Dementia Scale–Lite [RUD-Lite]) will be analyzed and reported separately from the CSR and are therefore not covered here. Similarly, the exploratory biomarker endpoints of changes in functional brain connectivity or changes in the integrity of white matter will be analyzed and reported separately from the CSR and are therefore not covered here.

The description of layouts for the CSR outputs, the details about the underlying analysis datasets and programs, and the linking of production outputs to sections in the CSR are not within the scope of this document and will be covered in the Data Analysis Plan Module 2 and 3.

The language used in this SAP supersedes that in the protocol and protocol synopsis. This SAP is based on Protocol version 4, issued on May 11, 2022.

1.1 OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, tolerability, and efficacy of long-term administration of open-label gantenerumab in participants with Alzheimer's Disease (AD) who completed GRADUATE I or GRADUATE II study. Specific objectives and corresponding endpoints for the study are outlined below.

Table 1 Objectives and Corresponding Endpoints

Primary Objective(s)	Corresponding Endpoint(s)
• To evaluate the safety and tolerability of long-term gantenerumab administered by SC injection	• Nature, frequency, severity, timing, and outcomes of adverse events and serious adverse events • Physical examinations (including neurologic systems), vital signs, ECG, laboratory tests, and Columbia-Suicide Severity Rating Scale (C-SSRS) • Nature, frequency, severity, and timing of ARIA-E and ARIA-H • Nature, frequency, severity, timing, and outcomes of ISRs • Incidence of treatment discontinuations for adverse events • Incidence of adverse events of special interest
Secondary Objective(s)	**Corresponding Endpoints**
• To evaluate the efficacy of long-term gantenerumab administered by SC injection	Change over time in cognition and/or function, as measured by the following: • Clinical Dementia Rating (CDR) • Mini-Mental State Examination (MMSE) • Alzheimer Disease Assessment Scale-Cognition, Subscale 11 (ADAS-Cog11) and Alzheimer Disease Assessment Scale-Cognition, Subscale 13 (ADAS-Cog13) • Verbal Fluency Task • Coding • Functional Activities Questionnaire (FAQ) • Alzheimer Disease Cooperative Study Group-Activities of Daily Living (ADCS-ADL)
Exploratory Objective(s): Efficacy	**Corresponding Endpoints**
• To evaluate the efficacy of long-term gantenerumab administered by SC injection	Change over time in: • Health-related quality of life, as assessed by the Quality of Life-Alzheimer's Disease (QoL-AD) scale • Behavioral and neuropsychiatric symptoms of AD, as measured by the Neuropsychiatric Inventory Questionnaire (NPI-Q)

	• Caregiver burden, as assessed by the Zarit Caregiver Interview for Alzheimer's Disease (ZCI-AD) scale • Elements of resource utilization, as assessed by the Resource Utilization in Dementia-Lite (RUD-Lite)
Exploratory Pharmacokinetic Objective(s)	**Corresponding Endpoints**
• To characterize the PK profile of gantenerumab administered by SC injection	• Plasma concentration of gantenerumab administered SC at specified timepoints
Immunogenicity Objective(s)	**Corresponding Endpoints**
• To evaluate the immune response to gantenerumab administered by SC injection	• Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study
Exploratory Biomarker Objective(s)	**Corresponding Endpoints**
• To evaluate the long-term effects of gantenerumab administered by SC injection	• Brain amyloid load over time, as measured by amyloid PET scan in a subset of participants • Brain tau load over time, as measured by tau PET scan in a subset of participants • CSF markers of disease over time in a subset of participants, including, but not limited to, $A\beta_{1-42}$, total tau (t-tau), and phosphorylated tau (p-tau) • MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures; changes in functional brain connectivity; or changes in the integrity of white matter in all participants • Blood and Plasma markers over time
Exploratory Health Status Utility Objective(s)	**Corresponding Endpoints**
• To evaluate the health status utility scores of participants treated with gantenerumab	• Health outcomes in participant and caregiver, as measured by EuroQol 5-Dimension Questionnaire (EQ-5D)

1.2 STUDY DESIGN

The POSTGRADUATE study is an open-label, multicenter, rollover study to evaluate the safety, tolerability, and efficacy of long-term administration of open-label gantenerumab

in participants with AD who completed GRADUATE I or GRADUATE II, either the double-blind or OLE part, as applicable (parent study).

To protect study data integrity and to aid the assessment of the long-term effects of gantenerumab, treatment assignment information from the double-blind phase of the parent GRADUATE I or GRADUATE II studies will remain blinded to the Sponsor, investigator, and participant at least until database lock of the parent studies, which will happen while this study is ongoing.

Participants who have completed the parent study GRADUATE I or GRADUATE II, either the double-blind or OLE part as applicable, will be eligible to participate in this study. Participants who discontinued early from study treatment during the parent study GRADUATE I or GRADUATE II, regardless of the reason, will not be eligible for this study.

Informed consent should be obtained from participants while they are in the parent study (GRADUATE I or GRADUATE II) including the safety follow-up, until a day before the first dose in POSTGRADUATE. In special situations, informed consent can be obtained at a later timepoint upon providing an appropriate rationale to the Sponsor, and it must be obtained before any study procedures in this study are performed.

The first administration of study drug in this study will be as follows:

- For participants who completed the double-blind part and did not enter the OLE part of GRADUATE I or GRADUATE II: The first administration of open-label study drug should take place approximately 2 weeks after the last efficacy and safety visit of the double-blind part of the parent study (GRADUATE I or GRADUATE II) and will be considered the OLE baseline visit (OLE Day 1).

- For participants who completed the double-blind part and the OLE part of GRADUATE I or GRADUATE II, the first administration of study drug in this study should take place approximately 2 weeks after the OLE Week 34 visit or the final dose visit in the GRADUATE I or GRADUATE II OLE. Participants who have a gap in their transition between the OLE part of the parent study (GRADUATE I or GRADUATE II) and this study, for unforeseen reasons, will roll over to this study continuing the schedule of activities as per their last visit in the OLE part of the parent study (GRADUATE I or GRADUATE II). Discussion with the Sponsor is recommended.

Participants with evidence of amyloid-related imaging abnormalities – edema/effusion (ARIA-E) on the last per-protocol study magnetic resonance imaging (MRI) scan report in GRADUATE I or GRADUATE II, either its double-blind or OLE part, as applicable, will be retained in GRADUATE I or GRADUATE II until the ARIA-E finding is resolved. They may then enroll in POSTGRADUATE. For those enrolling from the OLE part, the first

visit of the participants in POSTGRADUATE will be adapted according to the schedule of the visits of each participant in the parent study.

The data from the last visit in GRADUATE I or GRADUATE II (e.g., final efficacy and safety visit of the double-blind part or last visit in the GRADUATE I or GRADUATE II OLE part) will be used as the data for the first visit in this study if the two visits take place within 4 weeks of each other. All cognitive scales, and the Columbia-suicide severity rating scale (C-SSRS) do not need to be repeated if they were performed within 6 months in the previous parent study. The MRI scan does not need to be repeated if performed within 6 months in the previous parent study (GRADUATE I or GRADUATE II) and following the final study drug dose in the parent study. Vital signs and urine pregnancy test will have to be performed at the first visit in this study before dosing. MRI and urine pregnancy test results must be available before dosing.

In this study, participants who were in the active double-blind arm in the parent study (GRADUATE I or GRADUATE II) will continue receiving open-label gantenerumab 510 mg subcutaneously (SC) every two weeks (Q2W), and those participants who were in the placebo double-blind arm will go through a full up titration scheme while retaining the blinding to the previous treatment allocation. Details of the dosing scheme are described in Section 4.3.2 of the study protocol. If there is a delay in a participant's transition between the OLE part of the parent study (GRADUATE I or GRADUATE II) and this study (for instance, due to delays in the approval of this study at a site) that goes beyond a reasonable time frame as determined by the Sponsor, the participant may be asked to start at the dose they were at previously when they completed the parent study and to perform a safety MRI before receiving the target dose. In this case, such decisions will be made after discussion with the Sponsor.

The dosing schedule and the schedule of activities will be different for participants, depending on whether they completed the OLE part of GRADUATE I or GRADUATE II study, which covers the up titration phase for the participants in the placebo arm, or if they completed only the double-blind part. Details are described in Appendix 1 of the study protocol.

Following baseline assessments (i.e., OLE Day 1 either in this protocol or in the parent protocol), each participant will be treated for 4 years. The study duration has been extended from 2 to 4 years to collect more information on the long-term safety and tolerability of gantenerumab in AD and its efficacy in the context of long-term exposure and to increase the overall number of participant-years of exposure, thus increasing understanding of gantenerumab's long-term safety and efficacy profiles. Unless participants are eligible and choose to enroll in an alternative gantenerumab OLE study that becomes available, the final dose of study drug will be administered at OLE Week 206. At the end of the treatment period, all participants will undergo an OLE Week 208 visit. Participants will be asked to come back for a follow-up visit at OLE

Week 220 unless they are transitioning to an alternative gantenerumab OLE study that becomes available.

Participants who discontinue study drug at any time during this study will be asked to complete an early termination visit 2 weeks after their final dose and also return for collection of safety data (except safety MRI) and limited efficacy data (i.e., secondary endpoints) (see Section 4.6.1 of the study protocol) or to complete the safety follow-up period and all related assessments.

Participants who do not meet the criteria for participation in this study (screening failure) may be re-screened. The investigator will record reasons for screening failure in the screening log (Section 4.5.1 of the study protocol).

An interim analysis will be conducted at the time of the primary analysis for the GRADUATE parent studies, to support a potential filing of gantenerumab in case of positive read-out of the pivotal studies. The analysis will be considered strictly administrative and will not impact the conduct of the study, i.e., early termination for futility or efficacy will not be considered. The final analysis will take place after the last participant, last visit, occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last participant, whichever occurs later.

China Enrollment Plan

Based on historical data, participant recruitment is expected to take longer in China; therefore, a specific China enrollment plan has been established in the GRADUATE parent studies.

In the GRADUATE I study, after completion of the global enrollment phase, additional participants are being enrolled in an extended China extension phase at China's sites in mainland China to investigate the consistency in treatment effect between the China subpopulation and the global population for the purpose of registration in China.

The global population will include all participants enrolled during the global enrollment phase (including participants enrolled at China’s sites in mainland China, Hong Kong, and Taiwan, during that phase), and the China subpopulation will include all participants at China’s sites (i.e., during both the global enrollment phase and the extended China enrollment phase).

Separate analyses will be performed for the global population and the China subpopulation. The analysis of the China subpopulation will be conducted and reported separately from the analysis detailed in this SAP.

Substudies

The substudies associated with POSTGRADUATE will be described in separate protocols, and participants consenting to enroll in these substudies will be asked to sign the associated Informed Consent Forms. To date, two optional substudies are associated with POSTGRADUATE: a longitudinal amyloid PET substudy and a longitudinal tau PET substudy.

The amyloid and tau PET assessments will enable a longitudinal evaluation of the effect of gantenerumab on brain amyloid deposition as measured by florbetaben or flutemetamol PET radioligands and tau burden as measured by [^{18}F]GTP1 (Genentech Tau Probe 1; an investigational radioligand for in vivo imaging of tau protein aggregates) in participants with AD.

The collected PET data are expected to help in understanding the effects of gantenerumab on amyloid and tau pathology over time as well as the relationship between changes in florbetaben/flutemetamol/[^{18}F]GTP1-PET and changes in other endpoints in POSTGRADUATE.

1.2.1 Treatment Assignment and Blinding

This is a non-randomized, open-label study. An interactive voice or web-based response system (IxRS) will be used to manage participant enrollment and drug supply. After initial written informed consent has been obtained, the study site may obtain the participant's identification number. After all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's treatment assignment from the IxRS.

Participants randomized to the active treatment arm in the parent study (GRADUATE I or GRADUATE II) will continue to be administered the study drug every 2 weeks (Q2W administration of 510 mg SC gantenerumab). Participants randomized to the placebo arm in the parent study (GRADUATE I or GRADUATE II) will have to go through at least 34 weeks of uptitration. Participants, sites, and Sponsor will remain blinded to previous treatment allocation in the parent study (GRADUATE I or GRADUATE II) to protect study integrity.

To protect study data integrity and to aid the assessment of the long-term effects of gantenerumab, study site personnel and participants will be blinded to previous treatment assignment in the parent studies (GRADUATE I or GRADUATE II). The Sponsor and its agents will also be blinded to previous treatment assignment, at least until unblinding of the parent studies (GRADUATE I and GRADUATE II), which will happen while this study is ongoing, with the exception of individuals who require access to participant's treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers,

operational assay group personnel, IxRS service provider, and independent Data Monitoring Committee (iDMC) members.

Pharmacokinetics and immunogenicity samples will be collected from all participants, regardless of the treatment assignment. Laboratories responsible for performing study drug PK and anti-drug antibody (ADA) assays will be unblinded to participants' treatment assignments. Baseline immunogenicity samples will be analyzed for all participants.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which participant management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to participant unblinding, the investigator will be able to break the treatment codes by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment assignment code for all serious, unexpected suspected adverse reactions (see Section 5.7 of the study protocol) that are considered by the investigator or Sponsor to be related to study drug. The participant may continue to receive treatment, and the investigator, participant, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to participant treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

1.2.2 Independent Review Facility

MRI scans will be reviewed by a central MRI core laboratory, which will perform the diagnostic reads and assessments of MRI outcome measures. MRI scans should preferably be transferred to the central MRI core laboratory electronically. Data transfer from individual study sites to the central MRI core laboratory may take up to 7-10 days, if not done electronically. Upon receipt of the MRI scans from the study sites, the central MRI core laboratory will provide the diagnostic reads. MRI results must be made available to investigators prior to the dosing visit that the MRI corresponds to (refer to Section 5.1.2 of the study protocol for additional details on MRI safety management).

MRI facility qualification and scan quality control will be performed by the central MRI core laboratory.

In addition to any local reading according to local procedures and requirements, all MRI scans will be reviewed by an expert central reader within approximately 1 week of receipt and a report provided to the site. For the purposes of overall study relevant decisions and recommendations, results from the expert central reader will be used. Any time the central reader identifies a new MRI finding, the study center medical staff and the Sponsor will be rapidly notified (see Section 5.1.2 of the study protocol).

All MRI readings and volume measures will be conducted by the central reader.

1.2.3 Data Monitoring

The iDMC will evaluate participant safety on a regular basis. In addition to the data defined in the iDMC Charter (e.g., the incidence and nature of adverse events, serious adverse events, adverse events of special interest, ARIA-E, amyloid-related imaging abnormalities – hemosiderin deposition [ARIA-H], and injection site reactions [ISRs]), the iDMC will review all necessary cumulative data, including efficacy data if necessary, at regular intervals during the study. It is anticipated that these assessments will occur approximately every 3 months or as detailed in the iDMC charter. At the time of each review, the iDMC will make appropriate recommendations (e.g., the study should continue as planned, the safety risk management should be modified, the protocol should otherwise be amended, and enrollment should be held pending further safety evaluations).

Decisions will be made after considering the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details, such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities are detailed in the iDMC Charter.

Final decisions will rest with the Sponsor.

In the event the iDMC which reviews safety in both the parent studies (GRADUATE I and GRADUATE II) and POSTGRADUATE is no longer required (for instance after the unblinding of the parent studies) evaluation of participant safety may be taken over by the Sponsor's Internal Monitoring Committee (IMC), with details documented in an IMC Charter.

1.2.4 ARIA Management

In POSTGRADUATE, taking into account the evolving experience with managing ARIA findings, including the finding that continued gantenerumab treatment during episodes of asymptomatic mild ARIA-E was not associated with clinically unfavorable outcomes, the Sponsor intends to examine the safety of continuing gantenerumab treatment through mild to moderate asymptomatic ARIA-E findings and to examine the safety of gantenerumab therapy in the presence of an increased number of ARIA-H (microhemorrhages). In the parent studies, treatment was interrupted for participants

with asymptomatic ARIA-E with a BGTS ≥4 or symptomatic ARIA-E and discontinued for participants with more than 15 ARIA-H or with disseminated leptomeningeal hemosiderosis. In this study, ARIA management rules are based on the Bioclinica 5-point severity score (renamed as Severity Scale of ARIA-E (SSAE) since the writing of the study protocol) and treatment is interrupted for asymptomatic ARIA-E with a Bioclinica score ≥4 or symptomatic ARIA-E of any severity with CNS symptoms attributable to ARIA-E in the judgement of the investigator and discontinued for ARIA-H with disseminated leptomeningeal hemosiderosis. Disseminated leptomeningeal hemosiderosis is defined as more than three focal leptomeningeal hemosiderosis cumulatively.

2. STATISTICAL HYPOTHESES

All analyses provided in this document are descriptive, thus no statistical hypothesis will be tested in these analyses.

3. SAMPLE SIZE DETERMINATION

The sample size will be determined by the number of participants who complete the parent studies (GRADUATE I and GRADUATE II) and enroll in this study. The sample size is expected to be no more than approximately 2032 participants.

4. ANALYSIS SETS

The following analysis sets are defined:

Analysis Set	Definition
All enrolled participants	All enrolled participants (i.e.; who signed the informed consent form and are marked as enrolled in IxRS), whether or not the participant received the assigned treatment.
ITT (intent to treat)	All enrolled participants, who received at least one dose of study drug. Participants will be analyzed by the treatment they were randomized to in the parent studies.
Safety-evaluable (SE)	All participants enrolled who received at least one dose of study drug in this study or in the OLE part of the parent studies. Any participant randomized to placebo in the parent studies who received at least one dose (any dose) of active drug during the double-blind treatment in the parent studies will be summarized as having received the active drug in the parent studies.
MRI safety-evaluable (M-SE)	All participants in the safety-evaluable analysis set who had at least one post-baseline safety MRI scan.
Immunogenicity	All enrolled participants with at least one ADA assessment.
MRI modified intent-to-treat (MRI-mITT)	All participants in the ITT analysis set who had at least one valid volumetric MRI quantitative measurement.
CSF modified intent-to-treat (CSF-mITT)	All participants in the ITT analysis set who had at least one valid quantitative cerebrospinal fluid (CSF) measurement.

Amyloid PET modified ITT (aPET-mITT)	All enrolled participants of the ITT analysis set who consented to the Amyloid PET substudy, did not withdraw consent before enrolment in the substudy and had at least one amyloid PET scan with a valid quantitative measurement.
Tau PET modified ITT (tPET-mITT)	All enrolled participants of the ITT analysis set who consented to the Tau PET substudy, did not withdraw consent before enrolment in the substudy and had at least one tau PET scan with a valid quantitative measurement.

ITT = intent to treat; SE = safety-evaluable; M-SE = MRI safety-evaluable.

5. STATISTICAL ANALYSES

5.1 GENERAL CONSIDERATION

The purpose of this study is to assess the safety, tolerability, and efficacy of long-term administration of open-label gantenerumab in participants with AD who completed GRADUATE I or GRADUATE II.

The period of the POSTGRADUATE study and the OLE period from the parent studies will henceforth be referred to as the OLE period. Data from the OLE period, i.e., from OLE baseline (see Section 5.1.1 below for definition) to the end of study, will be summarized. Consequently, for participants who completed the OLE part of the parent studies and gave informed consent for the POSTGRADUATE study, the data collected in the OLE period of the parent studies will be included in the CSR of POSTGRADUATE. This will ensure that data from baseline and uptitration are included in the analyses for all participants of POSTGRADUATE. Participants of the OLE period of the parent studies without informed consent to POSTGRADUATE cannot be included in the analyses for the CSR of POSTGRADUATE and will instead be included in the analyses within the parent studies' CSRs.

All analyses will be purely descriptive and no imputation of missing data will be performed. For continuous data, descriptive statistics of mean, standard deviation, median, 1st and 3rd quartile as well as minimum and maximum and number of available data will be provided. For categorical data, number and frequency will be provided for each category as well as the number of available data.

All analyses of safety endpoints will be based on the SE analysis set unless mentioned otherwise while all analyses of efficacy endpoints will be performed for the ITT analysis set. The immunogenicity analysis set will be used for immunogenicity analyses.

Results will be shown separately based on previous treatment in the GRADUATE parent studies GRADUATE I and GRADUATE II, and by participation / non-participation in the OLE part of the parent studies and overall. For analyses using the ITT analysis set, this will be the treatment as randomized in the parent studies; for analyses using the SE analysis set, this will be the treatment actually received in the parent studies.

The results are shown separately by participation / non-participation in the OLE part of the parent studies to mitigate the introduction of bias into the overall results. The non-inclusion of participants who discontinued during the OLE part of the parent studies and do not have an informed consent to POSTGRADUATE introduces an immortal time bias in certain analyses for this group of participants for the OLE part of the parent studies. The separation is further required due to different ARIA management rules in the parent studies and this study.

5.1.1 Definition of Baseline

The first dosing visit in the OLE will be considered as baseline (OLE Day 1). The last available assessment made before or on OLE Day 1 will be considered the baseline assessment if occurring within 12 weeks before or on OLE Day 1 and prior to first dose for standard-of-care examinations or within 6 months for C-SSRS, cognitive scale results and MRI scans. For ADA data, baseline will be the baseline value of the parent studies to ensure that the baseline value is before any dose of the investigational product.

5.2 PARTICIPANT DISPOSITION

The analysis of participant disposition will be based on all enrolled participants (see analysis sets in Section 4). The number of participants enrolled will be tabulated by country and site. Participant disposition (the number of participants enrolled, treated, and completing the study) will be tabulated. Premature study drug discontinuation and study discontinuation, as well as reasons for discontinuations, will be summarized.

Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized. Separate tables will be provided for COVID-19-related major protocol deviations and reasons for COVID-19-related major protocol deviations.

5.3 PRIMARY ENDPOINTS ANALYSIS

5.3.1 Definition of Primary Endpoints

The primary objective for this study is to evaluate the safety and tolerability of long-term gantenerumab administered by SC injection on the basis of adverse events (AEs), physical examinations, vital signs, ECGs, laboratory tests, C-SSRS, ARIA-E and ARIA-H, ISRs, treatment discontinuations for AEs, and incidence of AEs of special interest.

The corresponding primary endpoints are:

- Nature, frequency, severity, timing, and outcomes of adverse events and serious adverse events
- Physical examinations (including neurologic systems), vital signs, ECG, laboratory tests, and Columbia-Suicide Severity Rating Scale (C-SSRS)
- Nature, frequency, severity, and timing of ARIA-E and ARIA-H

- Nature, frequency, severity, timing, and outcomes of ISRs
- Incidence of treatment discontinuations for adverse events
- Incidence of adverse events of special interest

The analytical approaches are described in pertinent subsection for each endpoint below.

5.3.2 Main Analytical Approach for Primary Endpoint(s)

All these safety analyses will be performed in the SE analysis set, except for analyses of ARIA-E or ARIA-H, CNS symptoms temporally associated with ARIA events or other MRI safety findings that will be based on the M-SE analysis set.

Participants will be analyzed according to the previous treatment they actually received in the parent studies and by participation / non-participation in the OLE part of the parent studies.

Descriptive statistics will be used to analyze all safety data collected in the study in the SE analysis set, unless otherwise specified.

Safety analyses will provide summaries of exposure to study treatment, adverse events, changes in laboratory test results (including shift tables), MRI findings, changes in vital signs and ECGs, and changes in C-SSRS scores as described in pertinent sections below.

5.3.3 Adverse Events

All verbatim AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version that is current at the time of the analysis (Version 25.0 or higher), and AE severity will be graded according to the scale defined in Table 3 in Section 5.3.3 of the study protocol (mild/moderate/severe). For each displayed participant group, the frequency of each AE preferred term will be defined as the number of participants experiencing at least one occurrence of the event. Each table will present the overall number and percentage of participants experiencing at least one AE and the total number of AEs reported. Percentages will be based on the number of participants in the SE analysis set. In summary tables, AEs will be sorted by body system (in decreasing order of overall incidence), then by preferred term (in decreasing order of overall incidence). The summary tables will be restricted to treatment-emergent AEs, i.e., AEs that occur or worsen on or after the day of first OLE dose, with onset no later than 14 weeks after last dose. Non-treatment-emergent AEs (AEs ongoing at OLE Day 1 with onset before the first OLE dose) and AEs occurring more than 14 weeks after the last dose will be listed.

The following safety information will be summarized:

- AEs, AEs by intensity, AEs related to study drug
- AEs with fatal outcome

- Serious AEs (SAEs), SAEs by intensity, SAEs related to study drug
- AEs leading to discontinuation of study treatment
- AEs leading to dose modifications (dose interruption, dose reduction, or delayed up-titration). Delayed up-titration at any given visit is defined as the simultaneous occurrence of the following two tickboxes in the eCRF Adverse Event form:
    - Action taken with open label gantenerumab due to SAE/AE: Dose Not Changed
    - If Dose not changed, was open label dose regimen modified from protocol schedule due to SAE/AE? Yes
- Injection site reaction (ISR) signs and symptoms
- Systemic injection reactions (AEs with “systemic reaction” selected)

Protocol-specified adverse events of special interest (AESI) will be listed.

The impact of the COVID-19 pandemic on the safety data will be assessed by reviewing the following:

- Confirmed or suspected COVID-19 AEs
- AEs associated with COVID-19
- Potential long COVID-19 symptoms

The following data handling rules will be applied for all AE summary tables:

- Events that are missing both onset and end dates will be considered to have started after the first dose of study drug and the duration will be set to missing.
- If the onset date is missing, and the end date is on or after the first dosing date or unresolved or missing, then the event will be considered to have started after the first dose of study drug.

The following data handling rules will also be applied for specific tables:

- An AE will be included in the summary table of AEs leading to study drug discontinuation if the “action taken with open label gantenerumab” drop-down menu on the AE eCRF is checked “drug withdrawn”.
- In the summary table of AEs by intensity, if a participant has more than one occurrence of an event, the event with the most severe intensity will be counted. If the intensity of an AE is missing, then the AE will be included only in the total number of events column, and not in the count of participants with the event by intensity.
- In the summary table of AEs related to study drug, if a participant has more than one occurrence of an event, the related event will be counted if applicable. If the relationship of an AE is missing, then the AE will not be included in the count of participants with the event by relationship

5.3.4 Magnetic Resonance Imaging Safety Findings

ARIA-E and ARIA-H are identified risks associated with gantenerumab. Sites were asked to capture ARIA findings as AEs in the POSTGRADUATE eCRF if they met any of the following criteria:

- Symptomatic ARIA-E (onset or worsening of CNS symptom[s] attributable to ARIA-E MRI findings in the judgement of the investigator), and/or
- ARIA findings that result in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation), and/or
- Findings that are otherwise clinically significant in the investigator's judgment

Not all ARIA MRI findings qualify as AE. ARIA analyses will be mainly based on ARIA MRI findings. ARIA AEs will also be reported. ARIA analyses will be restricted to ARIAs documented during this study or the OLE part of the parent studies.

Based on MRI data, the incidence, severity (based on the Bioclinica severity scale (see Appendix 2) and the Barkhof Grand Total Score [BGTS]) and timing of ARIA-E and the incidence and timing of ARIA-H will be summarized overall and also by APOE ε4 genotype (by number of alleles) and by dose level. For participants from the OLE part of the parent studies, only ARIA-E severity measured by the BGTS is available for events that occurred during the OLE part of the parent studies. The timing of ARIA-E and ARIA-H may be summarized by descriptive statistics. Recurrence of ARIA-E within this study or the OLE part of the parent studies will be summarized. ARIA-E with associated and attributable CNS symptoms (see Section 5.3.4.1) and serious associated and attributable CNS symptoms will be summarized overall and also by APOE ε4 genotype (by number of alleles). Temporal co-occurrence of ARIA-E and ARIA-H will be summarized overall and also by APOE ε4 genotype. Temporal co-occurrence is defined as an MRI scan showing new ARIA-H that occurs between ARIA-E onset and resolution (inclusive), irrespective of the brain region.

MRI findings other than ARIA will also be summarized.

5.3.4.1 CNS Symptoms Temporally Associated with and Attributable to ARIA-E MRI Findings

CNS symptoms temporally associated with and attributable to ARIA-E are defined as onset or worsening of CNS symptom(s) that is/are temporally associated with ARIA-E MRI findings and considered by the investigator to be attributable to ARIA-E. CNS symptoms experienced by the participant that are new or worsened since the last MRI without ARIA-E are collected in a CNS Symptoms Request Form. To identify CNS symptoms temporally associated with and attributable to ARIA-E MRI findings, the following definitions will be used:

NEW CNS symptoms: If there is any AE reported in the eCRF with 'Reported on this study's CNS Symptom Collection Form' = Yes that is [new since date of most recent MRI scan showing no ARIA-E findings] AND is [ongoing or ends between the date of most

recent site visit prior to date of MRI scan showing new ARIA-E (MRI) and date of MRI scan showing ARIA-E resolution (MRI)] AND has the question “Is this AE attributable to ARIA-E?” answered with Yes in the eCRF AE page, then ARIA-E should be classified as associated with attributable CNS symptoms

OR

WORSENED CNS symptoms: If there is any AE reported in the eCRF with ‘Reported on this study's CNS Symptom Collection Form’ = Yes that is [started before the date of most recent MRI scan showing no ARIA-E findings] AND is [ongoing or ends between the date of most recent site visit prior to date of MRI scan showing new ARIA-E (MRI) and date of MRI scan showing ARIA-E resolution from MRI data] AND [there is an increase in severity grading] AND has the question “Is this AE attributable to ARIA-E?” answered with Yes in the eCRF AE page, then ARIA-E should be classified as associated with attributable CNS symptoms.

The CNS symptoms temporally associated with and attributable to ARIA-E MRI findings will be listed and summarized overall and also by APOE ε4 genotype (by number of alleles). The same summary and listing will be produced for all CNS symptoms temporally associated with (but not necessarily attributable to) ARIA-E MRI findings.

5.3.5 Laboratory Data

Laboratory data will be summarized for each assessment visit using descriptive statistics of absolute values and change from baseline values. In addition, the frequency of patients with abnormal laboratory values will be summarized.

5.3.6 Vital Signs

Vital signs assessments include systolic blood pressure, diastolic blood pressure, and pulse rate measured throughout the study. Vital sign measurements will be summarized for each assessment visit using descriptive statistics of absolute values and change from baseline values. In addition, the frequency of patients with abnormal results will be summarized.

5.3.7 ECGs

ECG data will be summarized by previous treatment group and participation / non-participation in the OLE part of the parent studies for each assessment visit using descriptive statistics of absolute values and change from baseline values for the following parameters:

- Heart rate
- QRS duration
- RR interval
- PR interval

- QT interval

In addition, ECG overall interpretations will be summarized by previous treatment group, participation / non-participation in the OLE part of the parent studies and visit.

5.3.8 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a tool used to assess the lifetime suicidality of a participant (C-SSRS at baseline) as well as any new instances of suicidality (C-SSRS since last visit). The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual or potential lethality.

Suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent will be summarized by previous treatment group and participation / non-participation in the OLE part of the parent studies. In addition, change from baseline to worst post-baseline assessment in suicidality categories will be summarized by previous treatment group and participation / non-participation in the OLE part of the parent studies.

5.4 SECONDARY ENDPOINTS ANALYSES

According to the study protocol, section 6.5, the secondary efficacy analyses are planned to use all enrolled participants to investigate both the long-term efficacy and potential disease modifying effect of long-term gantenerumab. However, all analyses in this SAP will be restricted to efficacy endpoints collected under this study or during the OLE part of the parent studies and will be purely descriptive. No estimands will be defined.

Analyses of long-term effect of the study drug (across the double-blind and open label phases from the parent Study [GRADUATE I or GRADUATE II]) as well as efficacy analyses of delayed start of treatment are not subject to this SAP and will be described elsewhere.

5.4.1 Secondary Efficacy Endpoints

The secondary objective for this study is to evaluate the efficacy of long-term gantenerumab administered by SC injection on the basis of change over time in cognition, function, and other outcomes as measured by the following:

- Clinical Dementia Rating (CDR)
- Mini-Mental State Examination (MMSE)
- Alzheimer Disease Assessment Scale-Cognition, Subscale 11 (ADAS-Cog11) and Alzheimer Disease Assessment Scale-Cognition, Subscale 13 (ADAS-Cog13)
- Verbal Fluency Task
- Coding
- Functional Activities Questionnaire (FAQ)
- Alzheimer Disease Cooperative Study Group-Activities of Daily Living (ADCS-ADL)

Descriptive statistics will be provided for each of these endpoints, summarizing absolute values and change from baseline for each assessment time point by previous treatment group and participation / non-participation in the OLE part of the parent studies.

5.4.1.1 Clinical Dementia Rating

The CDR-Global Score (CDR-GS) characterizes a participant's level of impairment according to the following categories: 0 (normal), 0.5 (very mild dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia). The CDR-Sum of Boxes (CDR-SOB) score is a detailed quantitative general index that provides more information than the CDR-GS in participants with mild dementia (Berg 1988; Morris et al. 2001, O'Bryant et al. 2010) and is scored from 0 to 18 with higher scores indicating greater impairment. The CDR characterizes six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The necessary information to make each rating is obtained through a semi-structured interview with the participant and a reliable informant or collateral source (e.g., a caregiver).

Descriptive statistics will be provided for the CDR-SOB and the CDR-GS.

5.4.1.2 MMSE

The MMSE is a set of standardized questions used to evaluate possible cognitive impairment and help stage the severity level of this impairment (Folstein et al. 1975). The questions target six areas: orientation, registration, attention, short-term recall, language, and constructional praxis/visuospatial abilities. The MMSE is a participant-based assessment. The score ranges from 0 to 30, with lower values indicating a greater impairment.

5.4.1.3 ADAS-Cog11 and ADAS-Cog13

The ADAS-Cog is the most frequently used scale to assess cognition in clinical trials for mild to moderate AD dementia (Rozzini et al. 2007; Connor and Sabbagh 2008; Ihl et al. 2012). More specifically, the ADAS-Cog is a participant-based assessment that measures learning and memory, language production, language comprehension, constructional praxis, ideational praxis, and orientation. The modified version will be used; it has 13 items and includes the addition of delayed word recall and a number of cancellation subtests, as well as use of only one trial for word recognition (Mohs et al. 1997). Equivalent alternate forms of the word recall, word recognition, and number cancellation subtests will be used in successive test administrations. The ADAS-Cog 11 and 13 will be used in this study. Individual item scores are based on errors and generally range from 1 to 5, although some items have smaller or larger score ranges. The ADAS-Cog 13 total score ranges from 0 to 85, with higher scores reflecting greater impairment. It takes approximately 45 minutes to administer the ADAS-Cog 13.

5.4.1.4 Verbal Fluency Task

The category verbal fluency (e.g., animals) is a participant-based assessment that measures speed and flexibility of verbal thought. Verbal fluency tests are sensitive tools for detecting dementia (Pasquier et al. 1995; Lezak et al. 2004) and for monitoring decline over time (Clark et al. 2009).

5.4.1.5 Coding

The Coding, also called Digit Symbol Substitution Test (or DSST), is a subtest from the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV; Wechsler 2008). The Coding is a participant-based assessment that measures speed of processing and associative memory. The test is known to be sensitive to disease progression (Lezak et al. 2004). The 120-second version of the test will be used in this study.

5.4.1.6 FAQ

The FAQ (Pfeffer et al. 1982) is an informant-based measure of functional abilities. Informants provide performance ratings of the target person on ten complex higher-order activities. The FAQ is a 30-point scale, the higher the score the worse the performance.

5.4.1.7 ADCS-ADL

The ADCS-ADL (Galasko et al. 1997) is the scale most widely used to assess functional outcome in participants with AD (Vellas et al. 2008). The ADCS-ADL is a 23-item informant-based questionnaire that covers both basic activities of daily living (ADL) (e.g., eating and toileting) and more complex ADL or instrumental ADL (e.g., using the telephone, managing finances, preparing a meal). It has a 4-week recall period. Total scores range from 0 to 78, with higher scores indicating better functioning.

5.5 EXPLORATORY ENDPOINTS ANALYSIS

The exploratory efficacy analyses will be based on the ITT analysis set and will be restricted to efficacy endpoints collected under this study or during the OLE part of the parent studies. Therefore, analyses of long-term effect of the study drug (across the double-blind and open label phases from the parent study [GRADUATE I or GRADUATE II]) are not subject to this SAP and will be described elsewhere.

5.5.1 Exploratory Efficacy Endpoints

The exploratory efficacy objective is to evaluate the efficacy of long-term gantenerumab administered by SC injection in terms of change over time in:

- Health-related quality of life, as assessed by the Quality of Life-Alzheimer's Disease (QoL-AD) scale
- Behavioral and neuropsychiatric symptoms of AD, as measured by the Neuropsychiatric Inventory Questionnaire (NPI-Q)
- Caregiver burden, as assessed by the Zarit Caregiver Interview for Alzheimer's Disease (ZCI-AD) scale

- Elements of resource utilization, as assessed by the Resource Utilization in Dementia-Lite (RUD-Lite)

The RUD-Lite will be used in this study for informing pharmacoeconomic evaluations and will be reported separately. For the other endpoints, descriptive statistics will be provided for these endpoints by previous treatment group, participation / nonparticipation in the OLE part of the parent studies and assessment time point.

5.5.1.1 QoL-AD

The QoL-AD was developed to assess quality of life (QoL) in participants who have dementia (Logsdon et al. 1999, 2002). The QoL-AD consists of 13 items covering aspects of participants' relationships with friends and family, physical condition, mood, concerns about finances, and overall assessment of QoL. The total score is the sum of the 13 items and ranges from 13 to 52, with higher scores indicating better health-related QoL. In this study, the QoL-AD will be administered in a standardized, structured interview format to participants by investigative staff in order to gather participant responses about QoL. The caregiver will also complete the caregiver version of the questionnaire to enable proxy responses from the caregiver.

5.5.1.2 NPI-Q

The NPI-Q (Kaufer et al. 2000) was developed to assess a wide range of behaviors encountered in patients with dementia, to provide a means of distinguishing severity of behavioral changes, and to facilitate rapid behavioral assessment through the use of screening questions. It is an informant-based instrument in which 12 behavioral domains are evaluated. The recall period is the past month, and severity scores range from 0 to 36, with higher scores indicating greater severity. The caregiver's distress portion of the scale will not be used in this study.

5.5.1.3 ZCI-AD

ZCI-AD is a modified version of the Zarit Burden Interview, which was originally designed to reflect the stresses experienced by caregivers for people with dementia (Zarit and Zarit 1990). The modified version includes slight modifications in item and title wording (e.g., removal of "your relative" to refer directly to the participant, removal of "burden" from title) and the use of 11-point numerical rating scales. The ZCI-AD scale consists of 30 items and is completed by the caregiver without involvement from the site staff. It has a 4-week recall period.

5.6 OTHER SAFETY ANALYSES

5.6.1 Extent of Exposure

Exposure to study drug information will be summarized descriptively as follows:

- Treatment duration (in weeks)
- Total number of administrations
- Total cumulative dose (mg)
- Number of participants with any dose administration, separately for each dose level

5.7 OTHER ANALYSES

5.7.1 Summaries of Conduct of Study

The summary of study conduct will include a description of the following items by previous treatment group and participation / non-participation in the OLE part of the parent studies:

- Number of participants enrolled
- Number of participants included in each analysis set
- Number and percentage of participants who prematurely withdrew from the study or from study treatment (including the reasons for discontinuation and the distribution of these discontinuations by time-windowed visit)
- Incidence of protocol deviations – overall and by four main categories (inclusion criteria, exclusion criteria, medication and procedural)
- Number of participants with home nursing

Major protocol deviations and premature withdrawals will be listed.

5.7.2 Summaries of Demographics and Baseline Characteristics

Demographic and baseline characteristics (such as age, sex, race, disease stage at enrolment in the parent studies, stratification factors as reported in IxRS at randomization in the parent studies, APOEe4 status (carrier vs non-carriers and APOe4 allele's status), presence and cumulative number of ARIA-H (during the screening and double-blind part of the parent studies), history of ARIA-E in the double-blind part of the parent studies, and use and non-use of background therapy for AD at OLE baseline, participation in POSTGRADUATE PET substudies) will be summarized descriptively for the ITT and SE analysis sets.

Descriptive summaries of continuous data will present the mean, standard deviation, median, and minimum and maximum. Descriptive summaries of discrete data will include frequencies expressed in terms of number and percentage of participants.

5.7.3 Summaries of COVID-19 Impact on the Trials

The POSTGRADUATE study is ongoing during the COVID-19 pandemic. Consequently, to monitor the potential impact of the pandemic on the trial, we will provide a specific set of descriptive analyses related to COVID-19 by previous treatment arm and participation / non-participation in the OLE part of the parent studies for the ITT analysis set (see Section 4), including:

- Demographic and Baseline Characteristics in Participants with Confirmed/ Suspected COVID-19 (see Section 5.7.2)
- COVID-19 AEs (see Section 5.3.3)
- COVID-19 related Protocol Deviations (see Section 5.2)
- Missed doses due to COVID-19

- Study discontinuations due to COVID-19
- Remote scale administrations

5.7.4 Immunogenicity Analyses

Immunogenicity analyses include the evaluation for antibodies against gantenerumab (i.e., ADAs), including the determination of antibody titers if appropriate. The immunogenicity analysis set will consist of all participants with at least one ADA assessment. The results of the confirmatory assay will be presented as a frequency table summarizing results at parent study baseline and during this study or the OLE part of the parent studies.

A listing of participants with positive ADA status per confirmatory assay and titer result will be provided.

Prior to completion of the study, one or more separate cutoff date(s) for ADA samples may be established to allow expedient samples analyses and early access by third party vendors.

5.7.5 Biomarker Analyses

Biomarker data will be summarized for each assessment visit using descriptive statistics of absolute values as well as change from baseline values. Plasma biomarker reports will be based on the ITT analysis set. All analysis including CSF biomarkers will be based on the CSF-mITT analysis set. The following pharmacodynamic biomarkers will be analyzed:

- Cerebrospinal Fluid (CSF):
  - Total tau (tTau)
  - Phosphorylated tau (pTau 181)
  - Neurogranin
  - Neurofilament (NFL)
- Plasma:
  - Phosphorylated tau (pTau 181)
  - Amyloid-beta 42 (Abeta-42)
- MRI-derived measurements, including:
  - Volumetric changes in whole brain, ventricles, hippocampus, cortical gray or other structures

In addition, other exploratory biomarkers will be reported separately.

5.7.6 Amyloid PET Substudy

The main objective of the POSTGRADUATE longitudinal amyloid PET substudy is to assess changes in brain amyloid load (as measured by florbetaben or flutemetamol) over time during the treatment with gantenerumab.

The analyses described here are restricted to analyses of data assessed during this study or during the OLE part of the parent studies. Analyses across the double-blind part of the parent studies and this study will be reported separately and are not subject of this SAP. This document will focus on amyloid PET data assessed during this study or during the OLE part of the parent studies.

5.7.6.1 Brain Amyloid Load Analysis

Two amyloid PET ligands are allowed in this substudy according to country and site availability: florbetaben and flutemetamol. However, the same ligand has to be used for the same participant throughout the study. For all participants, the ligand that is used has to remain the same as that used previously (e.g., if a participant has been enrolled in the parent study (GRADUATE I or GRADUATE II) with a positive florbetaben PET scan, only florbetaben will be allowed and used for the longitudinal follow-up scans for this participant in this study).

Centiloid mapping will be completed for the Standard Uptake Value Ratio (SUVR) data from the two amyloid PET ligands. The aPET-mITT analysis set will be used to summarize amyloid load in centiloid by descriptive statistics for each assessment time point as well as the change from baseline by previous treatment.

5.7.6.2 General Considerations on Amyloid PET Statistical Analyses

The baseline assessment will be the last amyloid PET scan before or on OLE Day 43 (time window for day 1 is +42 days) that was performed within 6 months before OLE Day 1.

With the Centiloid endpoint, data from both tracers will be pooled and analyzed together. Separate analysis by tracer with the Centiloid endpoint may also be conducted as appropriate.

Missing values will not be imputed.

Visit Windowing

The analysis of amyloid PET data will be undertaken using reporting windows as defined in

Table 2. In case of more than one assessment within a time window, the assessment with the date closest to the target (scheduled) day will be selected. The time windows are based on study days, defined as days on study since first OLE dose, with the day of first OLE dose being study Day 1 and the day before first dose being study Day -1

Because of visit windowing, data collected at an early termination visit will be summarized at the appropriate time in the trial. For participants who have discontinued treatment early, if a PET scan is performed more than 56 days (early termination visit expected 14 days after last dose, followed by time window per protocol for early termination is ±42 days) after the date of last dose, the PET scan will not be used for the analysis

Table 2 Time Windows for Amyloid PET Endpoints

Visit	Target study day	Time window
Baseline	1	-183, 43
Week 52	365	281, 449
Week 104	729	645, 813
Week 156	1093	1009, 1177
Week 208	1457	1373, 1541

Details for Definition of Variable

The Centiloid variable will be used rather than the original SUVR, because it allows data to be combined from different tracers, by mapping SUVR values to a standardized scale. The Centiloid variable is the current common standard in the scientific community.

The primary SUVR measure of interest is computed using a weighted composite target region and whole cerebellum as reference region. The weighted composite target region is composed of (both left and right side):

- frontal lobe,
- parietal lobe,
- temporal lobe lateral,
- cingulum posterior and
- anterior cingulate gyrus

Each region is weighted by its own volume. The Centiloid conversion is a linear transformation of SUVR with tracer-specific parameters that are given below in Table 3:

Centiloid Equation:

$$CL = SlopeCL \times SUVR + InterceptCL$$

CL=Centiloids; SlopeCL=slope; SUVR=standard uptake value ratio of the target region; InterceptCL=intercept.

The pertinent values for the two tracers are:

Table 3 Primary Centiloid Equation Parameters

Tracer	Reference	Slope	Intercept
Florbetaben-F18	whole cerebellum	175.6	-174.2
Flutemetamol-F18	whole cerebellum	143.5	-141.1

5.7.6.3 Summaries of Conduct of Substudy

The summary of study conduct will include a description of the following items by previous treatment arm:

- Number of participants enrolled
- Number of participants included in each substudy analysis set
- Number and percentage of participants who prematurely withdrew from the study, substudy or from study treatment (including the reasons for discontinuation and the distribution of these discontinuations by time-windowed visit)
- Incidence of protocol deviations – overall and by four main categories (inclusion criteria, exclusion criteria, medication and procedural)

Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized and listed. Separate tables will be provided for COVID-19-related major protocol deviations and reasons for COVID-19-related major protocol deviations.

Premature study drug discontinuation and study or substudy discontinuation, as well as reasons for discontinuations, will be summarized and listed.

The outputs will be performed on the Amyloid ITT analysis set.

5.7.6.4 Summaries of Demographic and Baseline Characteristics

Demographic and baseline characteristics of the participants who participate in this substudy will be summarized for the amyloid ITT analysis set as described in Section 5.7.2.

5.7.6.5 Safety Analyses

The safety analyses for the participants in the amyloid PET substudy will be conducted as part of the main study (POSTGRADUATE or OLE part of the parent study) safety analyses. There will not be a separate analysis of participants in this substudy.

5.7.6.6 Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one or more interim analyses for administrative reasons which may include efficacy, safety, and biomarker outcomes. No interim analysis of the substudy is planned for the time of the completion of parent studies.

5.7.7 Tau PET Substudy

The main objective of the POSTGRADUATE longitudinal tau PET substudy is to assess changes in brain tau load (as measured with [18F]GTP1) over time during treatment with gantenerumab.

The analyses described here are restricted to analyses of data assessed during this study or during the OLE part of the parent studies. Analyses across the double-blind part of the parent studies and this study will be reported separately and are not subject of this SAP. This document will focus on tau PET data assessed during this study or during the OLE part of the parent studies.

5.7.7.1 Brain Tau Load Analysis

The substudy is performed with an intravenous (IV) injection of a minimum of 185 MBq (5 mCi) and up to 259 MBq (not more than 7 mCi) of [^{18}F]GTP1 and imaging for a 30-minute scan, beginning 60 minutes following injection per PET scan.

The Tau ITT analysis set will be used to summarize tau burden in SUVR by descriptive statistics for each assessment time point as well as the change from baseline by previous treatment.

5.7.7.2 General Considerations on Tau PET Statistical Analyses

The baseline assessment for tau PET is scheduled for the OLE Day 1 visit (+42 days). Note that the results of the tau PET scan do not need to be available before dosing.

The last tau PET scan available within 6 months before OLE Day 1 and up to OLE Day 43 will be considered the baseline assessment.

Visit Windowing

For tau PET assessments, due to the long time between scheduled assessments, time windows, as defined in Table 4, will be used.

Table 4 Time Windows for Tau PET Endpoints

Visit	Target study day	Time window
Baseline	1	-183, 43
Week 52	365	281, 449
Week 104	729	645, 813
Week 156	1093	1009, 1177
Week 208	1457	1373, 1541

Details for Definition of Variable

Statistical analyses will be conducted on tau PET Median Standardized Uptake Value Ratios (SUVR) in the following four target regions of interest. In composite target regions, each region is weighted by its own volume.

- A temporal composite target region. This region is composed of (both left and right):
  - anterior and posterior superior temporal gyrus,
  - posterior temporal lobe,
  - fusiform gyrus,
  - middle and inferior temporal gyrus.
- A medial temporal composite region not including the hippocampus, composed of (both left and right):
  - Amygdala,
  - Parahippocampus,
  - Anterior medial and lateral temporal lobe.
- Frontal lobe (both left and right)
- Parietal lobe (both left and right)

The inferior cerebellar grey matter will be used as reference region for the calculation of median SUVRs for all four target regions considered.

5.7.7.3 Summaries of Conduct of Substudy

The summary of study conduct will include a description of the following items by previous treatment arm:

- Number of participants enrolled
- Number of participants included in each substudy analysis set

- Number and percentage of participants who prematurely withdrew from the study, substudy or from study treatment (including the reasons for discontinuation and the distribution of these discontinuations by time-windowed visit)
- Number and percentage of participants who completed treatment, the substudy, the study
- Incidence of protocol deviations – overall and by four main categories (inclusion criteria, exclusion criteria, medication and procedural)

Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized and listed. Separate tables will be provided for COVID-19-related major protocol deviations and reasons for COVID-19-related major protocol deviations.

Premature study drug discontinuation and study or substudy discontinuation, as well as reasons for discontinuations, will be summarized and listed.

The outputs will be performed on the Tau ITT analysis set.

5.7.7.4 Summaries of Demographic and Baseline Characteristics

Demographic and baseline characteristics of the participants who participate in this substudy will be summarized for the Tau ITT analysis set as described in Section 5.7.2.

5.7.7.5 Safety Analyses

The safety analyses for the participants in the tau PET substudy will be conducted as part of the main study (POSTGRADUATE or OLE part of the parent study) safety analyses. There will not be a separate analysis of participants in this substudy.

5.7.7.6 Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one or more interim analyses for administrative reasons which may include efficacy, safety, and biomarker outcomes. No interim analysis is planned for the substudy for the time of the completion of parent studies.

5.8 INTERIM ANALYSES

5.8.1 Planned Interim Analyses

A first interim analysis will be conducted at the time of the primary analysis for the parent pivotal studies GRADUATE I and GRADUATE II, to support a potential filing of gantenerumab in case of positive read-out of the pivotal studies. A second interim analysis may be conducted for an update on safety data in the filing dossier. The analyses will be strictly descriptive and will not impact the conduct of the study, i.e., early termination for futility or efficacy will not be considered. As this study is open-label and all analyses are descriptive, the interim analyses are considered of an administrative nature and will not have an impact on the final study results.

The following will be included in the interim analyses:

- Participant disposition (see Section 5.2)
- Demographics and baseline characteristics (see Section 5.7.2)
- Extent of exposure (see Section 5.6.1)
- Adverse Events (see Section 5.3.3)
- MRI safety findings (see Section 5.3.4, excluding analyses of time to onset or time to recurrence of ARIA, and analyses by dose level. Not all analyses will be run by APOE ε4 genotype.)
- Laboratory data (see Section 5.3.5)
- Vital signs (see Section 5.3.6)
- ECG data (see Section 5.3.7)
- C-SSRS data (see Section 5.3.8)

Immunogenicity analyses may also be performed at the interim analysis.

No interim analyses of efficacy data will be done.

5.8.2 Optional Interim Analyses

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one or more additional interim analysis(es) which may include efficacy, safety, and biomarker outcomes.

6. SUPPORTING DOCUMENTATION

Refer to Appendix 1 and Appendix 2 below.

Appendix 1 Changes to Protocol-Planned Analyses

All analyses in this SAP will be restricted to data collected under this study or during the OLE part of the parent studies and will be purely descriptive. No estimands will be defined.

Analyses of any long-term effect of the study drug (across the double-blind and open label phases from the parent study [GRADUATE I or GRADUATE II] and this study) are not subject to this SAP and will be described elsewhere.

Appendix 2 Bioclinica Severity Score

In order to determine the radiological severity of an ARIA-E event, the Bioclinica 5-point scale (Bracoud et al. 2017) will be used which has been renamed as Severity Scale of ARIA-E (SSAE) since the writing of the protocol. Please note that in addition to the 5-point scale being used for this study, a 3-point scale also exists.

Table 1 below details the definition of both the 5-point and 3-point severity scales.

Table 1 Bioclinica 3-Point and 5-Point Scale Definition

ARIA-E Extent	ARIA-E Focality	3-Point Scale (SSAE-3)	5-Point Scale (SSAE-5)
No ARIA-E	N/A	0	0
< 5 cm	Monofocal	1 (Mild)	1 (Mild)
	Multifocal	2 (Moderate)	2 (Mild +)
5−10 cm	Monofocal		3 (Moderate)
	Multifocal		4 (Moderate +)
> 10 cm	Monofocal	3 (Severe)	5 (Severe)
	Multifocal		

N/A = not applicable.

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