This supplement to Salloway S, et al. contains the following items:

1. Phase 3 Trial EMERGE: Study 302
    - Summary of changes
    - Original protocol: EMERGE_221AD302 Protocol V1 Final 09Apr15_Redacted
    - Final protocol: EMERGE_221AD302 Protocol V6.0 Final 28Jun2018_Redacted
    - Original SAP: EMERGE_221AD302_SAP_final_v1.0_Redacted
    - Final SAP: EMERGE_221AD302_SAP_v1.0_addendum_v1.0_final_Redacted
2. Phase 3 Trial ENGAGE: Study 301
    - Summary of changes
    - Original protocol: EMERGE_221AD301 Protocol V1 Final 09Apr15_Redacted
    - Final protocol: EMERGE_221AD301 Protocol V6.0 Final 28Jun2018_Redacted
    - Original SAP: EMERGE_221AD301_SAP_final_v1.0_Redacted
    - Final SAP: EMERGE_221AD301_SAP_v1.0_addendum_v1.0_final_Redacted

1. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

1.1. Changes in the Conduct of the Study

Participant enrollment into Study 221AD302 began under Version 1 dated 09 April 2015. Subsequently, there have been 5 amendments to the protocol, of which 4 amendments were submitted globally. Version 2 was not submitted globally and no participants were enrolled under this version. Protocol Version 6 (dated 28 June 2018) was in effect when the study was terminated.

A high-level summary of key changes to the global protocol is provided in Table 1, including key changes in ARIA management and changes affecting aducanumab dosing.

1.2. Changes in the Planned Analyses

The SAP Version 1 was finalized on 11 September 2018. A SAP Addendum was finalized on 04 November 2019, prior to database lock. The SAP Addendum documented the changes in the primary analysis and additional supplementary analyses as a result of the study termination. More specifically, the primary efficacy analysis excluded data collected after 20 March 2019 and supplementary analyses that included data after 20 March 2019 were added to evaluate the robustness of the primary analysis.

Table 1: Summary of Key Changes to Protocol 221AD302

Version[1]	Key Changes to ARIA Management	Other Key Changes
Version 1 (dated 09 April 2015) to Version 3 (dated 21 July 2016)	• To allow participants who suspend dosing after a first observance of ARIA to (a) restart at the same dose (rather than at the next lower dose per Version 1) after ARIA resolution and (b) titrate up to the originally assigned dose (rather than continue on the next lower dose for the duration of the study) • Removed requirement to permanently discontinue treatment after severe symptomatic ARIA or serious ARIA ("other medically important" criteria only); instead, in such participants, dosing could be suspended and then resumed at the same dose after ARIA and symptoms resolved or stabilized. • Regarding the management of recurrent ARIA, the amendment (a) allowed participants who had suspended dosing after a second episode to restart dosing, after ARIA resolution, at the next lower dose and continue uptitration (rather than remaining on the restart dose as in Version 1) and (b) required treatment discontinuation after	

Version[1]	Key Changes to ARIA Management	Other Key Changes
	3 ARIA episodes (rather than requiring a third dose reduction with Sponsor approval).	
Version 3 (dated 21 July 2016) to Version 4 (dated 24 March 2017)	• To allow ApoE ε4 carrier participants randomized to aducanumab high-dose to receive the same aducanumab high-dose regimen already received by ApoE ε4 noncarriers (i.e., per this amendment, the high-dose for carriers was changed from 6 to 10 mg/kg, which was also the high-dose for noncarriers).	
Version 4 (dated 24 March 2017) to Version 5 (dated 18 September 2017)		• To update the percentage of primary endpoint data estimated to be available at the time of a potential blinded sample size re-estimation. • To provide additional details on the planned sample size re-estimation (including the maximum potential sample size). • To add information on an additional concentration and formulation for aducanumab used in the study.
Version 5 (dated 18 September 2017) to	• To reflect the agreement of the data monitoring committee that the characteristics or outcomes of the	• To extend the study such that participants nearing study completion under Protocol Version 5 can

Version[1]	Key Changes to ARIA Management	Other Key Changes
Version 6 (dated 28 June 2018)	first event and recurrent events of ARIA were similar, the management of recurrent ARIA was modified so that a third episode of ARIA that requires dose suspension will no longer require study treatment discontinuation, and after recurrent ARIA resolves or stabilizes, dosing will resume at the same dose.	continue in the study and receive treatment until either the participant's End of Treatment Visit at Week 338 (an additional 3 years of treatment) or until the last participant has had his or her Week 182 Visit, whichever occurs first. • To update adjust the sample size consistent with an increase from 450 to 535 participants per treatment group following the blinded sample size re-estimation to ensure adequate power to detect a mean treatment effect of 0.5 for the primary endpoint, as prespecified in Protocol Version 1.

[1] No participants were consented under Protocol Version 2, and as a result, changes from Version 1 to Version 2 are not provided.

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PROTOCOL NUMBER: 221AD302

PHASE OF DEVELOPMENT: 3

PROTOCOL TITLE: A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease

EUDRA CT NO: **2015-000967-15**

DATE: 09 April 2015
Version 1.0
Final

SPONSOR SIGNATURE

Protocol 221AD302 was approved by:

PPD

09 APRIL 2015

Date

Biogen MA Inc.

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1. SPONSOR INFORMATION

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Please refer to the Study Reference Manual for complete contact information.

Biogen may transfer any or all of its study-related responsibilities to a contract research organization (CRO) and other third parties; however, Biogen retains overall accountability for these activities.

2. LIST OF ABBREVIATIONS

12F6A	recombinant, human anti-β-amyloid immunoglobulin G_1 monoclonal antibody with an amino acid sequence identical to aducanumab , produced in a different Chinese hamster ovary cell line
^{18}F-florbetapir	Also known as florbetapir-fluorine-18 or ^{18}F-AV-45 (amyloid ligand; trade name Amyvid)
Aβ	β-amyloid
AA	Alzheimer's Association
AD	Alzheimer's disease
ADA	antidrug antibodies
ADAS-Cog 13	Alzheimer's Disease Assessment Scale - Cognitive Subscale (13 items)
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment version)
AE	adverse event
ALT	alanine aminotransferase
ApoE	apolipoprotein E
ApoE ε4	apolipoprotein E4
ARIA	amyloid related imaging abnormalities
ARIA-E	amyloid related imaging abnormality-edema
ARIA-H	amyloid related imaging abnormality-hemorrhage or superficial siderosis
ASL-MRI	arterial spin labeling magnetic resonance imaging
AST	aspartate aminotransferase
CDR	Clinical Dementia Rating
ch12F6A	murine IgG_{2a} chimeric version of 12F6A or aducanumab
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	diastolic blood pressure
DHA	Directions for Handling and Administration
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
EDC	electronic data capture
EOT	End of Treatment
EQ-5D	EuroQol health status measure
ET	Early Termination
FU	follow-up

GCP	Good Clinical Practice
HbA_{1c}	glycosylated hemoglobin
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
Ig	immunoglobulin
IR	informant rated
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous(ly)
IWG	International Working Group
LTE	long-term extension
LP	lumbar puncture
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-model repeated measures
MMSE	Mini-Mental State Examination
MOCA	Montreal Cognitive Assessment
mPDQ-20	Perceived Deficits Questionnaire-20 modified version
MRI	magnetic resonance imaging
NIA	National Institute on Aging
NPI-10	Neuropsychiatric Inventory-10
PET	positron emission tomography
PK	pharmacokinetic(s)
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
SABR	Safety and Benefit-Risk
SAE	serious adverse event
SAP	statistical analysis plan
SB	sum of boxes
SBP	systolic blood pressure
SD	standard deviation
SR	subject rated
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
tf-fMRI	task free functional MRI
UV	unscheduled visit

3. SYNOPSIS

Protocol Number:	221AD302
Protocol Title:	A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease
Version Number:	1.0
Name of Study Treatment:	Aducanumab (BIIB037)
Study Indication:	Alzheimer's Disease
Study Rationale:	The purpose of this Phase 3 study is to assess the efficacy and safety of aducanumab compared with placebo in subjects with early Alzheimer's Disease (AD), including mild cognitive impairment (MCI) due to AD and a subset of mild AD. Aducanumab is a human monoclonal antibody that recognizes aggregated forms of β-amyloid (Aβ), including soluble Aβ oligomers and deposited fibrillar Aβ. Interim analyses of the ongoing multiple dose study (Study 221AD103) have demonstrated target engagement, a pharmacodynamic effect on amyloid reduction, and an effect on the Clinical Dementia Rating (CDR)-Sum of Boxes (SB) and Mini-Mental State Examination (MMSE) suggestive of a reduction in the progression of clinical impairment for aducanumab-treated subjects. These results along with the observed safety and tolerability profile warrant further Phase 3 investigation of aducanumab in a patient population spanning the early stages of the AD continuum.
Phase of Development:	3
Study Objectives and Endpoints (placebo-controlled period of the study):	The primary objective of the study is to evaluate the efficacy of monthly doses of aducanumab in slowing cognitive and functional impairment as measured by changes in the CDR-SB score as compared with placebo in subjects with early AD. The primary endpoint that relates to this objective is the change from baseline in CDR-SB score at Week 78

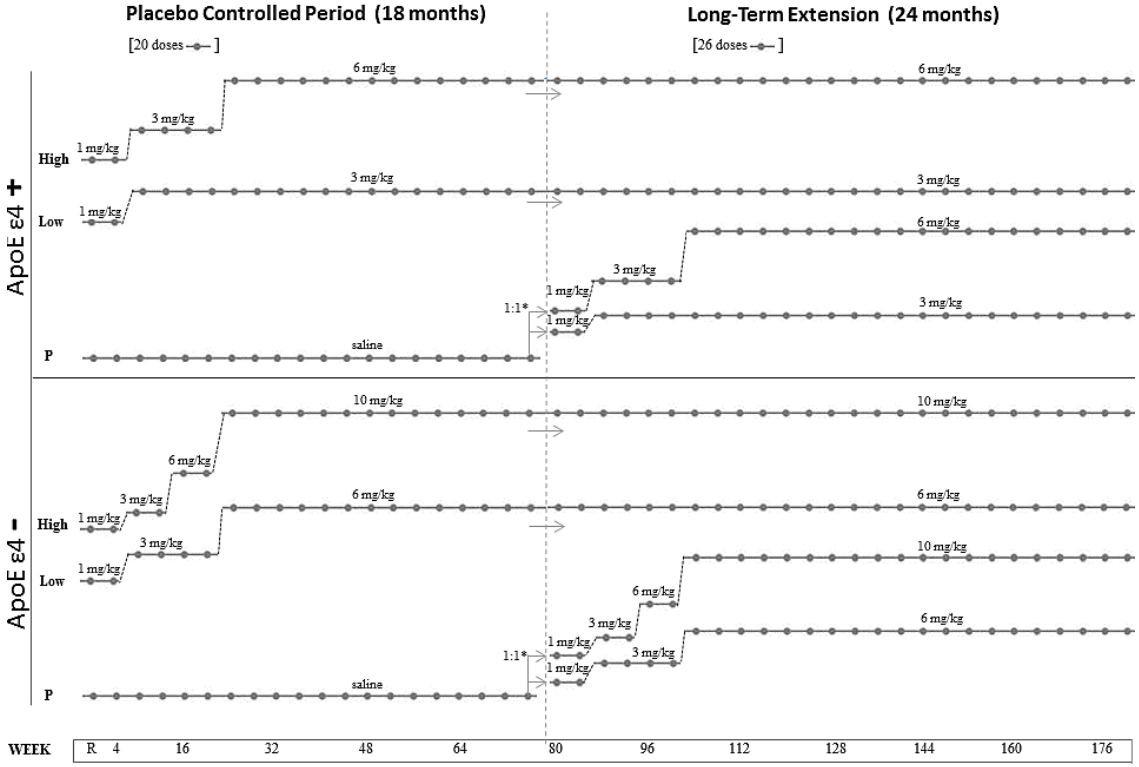
	Secondary objectives and endpoints are as follows: To assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by • MMSE – Change from baseline in MMSE score at Week 78 • Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13] – Change from baseline in ADAS-Cog 13 at Week 78 • Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI] – Change from baseline in ADCS-ADL-MCI score at Week 78 Tertiary objectives of this study are listed in Section 6.3.1. Tertiary endpoints of this study are listed in Section 6.3.2.
Study Objectives and Endpoints (Dose-Blind Long-Term Extension):	The objectives are to evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD, and to evaluate the long-term efficacy of aducanumab treatment as measured by clinical, radiological and additional assessments reported by the subject and informant/care partner. Endpoints for the LTE period of the study are listed in Section 6.4.2.
Study Design:	Multicenter, randomized study with an 18-month double-blind, placebo-controlled period followed by an optional 24-month dose-blind, LTE period
Study Location:	Approximately 150 sites globally
Number of Planned Subjects:	Approximately 1350 subjects will be enrolled
Study Population:	This study will be conducted in subjects with early AD, including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD according to NIA-AA

	criteria. Subjects must be positive for amyloid pathology as measured by amyloid positron emission tomography scan. Subjects must be 50 to 85 years old, and apart from the clinical diagnosis of early AD, they must be in good health as determined by the Investigator, based on medical history and the Screening assessments. Subject enrollment will be monitored so that approximately 60% to 70% ApoE ε4 carriers are enrolled. Enrollment will also be monitored, via interactive response technology (IRT), such that subjects with mild AD represent a small percentage of the total enrolled in the trial. Detailed criteria are described in Section 8.
Treatment Groups:	For the 18-month placebo-controlled period of the study and based upon their ApoE ε4 carrier status, subjects will be assigned to 1 of 3 treatment groups (450 subjects each) in a 1:1:1 ratio (aducanumab low dose: aducanumab high dose: placebo) as follows: **ApoE ε4 carrier** **Low dose (3 mg/kg)** **High dose (6 mg/kg)** **Placebo** **ApoE ε4 non-carrier** **Low dose (6 mg/kg)** **High dose (10 mg/kg)** **Placebo** After completion of the placebo-controlled period, subjects may enter a 24-month dose-blind LTE study during which all subjects will receive aducanumab.
Duration of Treatment and Follow-up:	Study duration for each subject participating in the placebo-controlled period only will be approximately 102 weeks (up to an 8 week Screening Period, 76 weeks of placebo or aducanumab dosing, and 18 weeks of follow-up). For subjects who enter the optional LTE, the total duration will be approximately 206 weeks or 47 months (up to an 8 week Screening Period, 76 weeks of placebo or aducanumab dosing, 4 weeks of follow-up, 100 weeks of dose-blind aducanumab dosing, and 18 weeks of follow-up).

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY 221AD302

4.1. Study Schematic

Figure 1: Study Design



ApoE ε4 +/- = apolipoprotein E4 positive/negative; R = randomization date

*Subjects who are assigned to placebo during the placebo-controlled period and are continuing into the LTE will be randomized in a 1:1 ratio to high and low dose aducanumab treatment (based upon their ApoE ε4 carrier status).

4.2. Schedule of Events

Table 1: Placebo-Controlled Period Schedule

Study Week	Screening (≤ 60 days before Day 1)[1]																											UV for a change in AD medication	FU/ET[2]
				Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	50	52	56	60	64	68	72	76	78 (EOT)		94
Study Day	V1	V2	V3	1	29 ± 3	57± 3	85 ±3	113 ±3	141 ±3	169 ±3	183 ±3	197 ±3	225 ±3	253 ±3	281 ±3	309 ±3	337 ±3	351 ±3	365 ±3	393 ±3	421 ±3	449 ±3	477 ±3	505 ±3	533 ±3	547 ±3		659 ±7
Initial Screening Consent[3]	X																												
Full Informed Consent[4]	X																									X[5]			
Eligibility Criteria	X			X																						X[5]			
Medical History	X																												
Alcohol/Drug Screen	X																												
HbA_{1c}	X																												
HIV/Hepatitis/ Coagulation	X																												
ApoE genotyping	X																												
DNA (optional)[6]	X																												
Height	X																												
Body Weight	X			X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X			X
Serum Pregnancy Test[7]	X																												
Urine Pregnancy Test[7]				X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X			X
Physical Examination	X						X			X							X							X		X		X

Study Week	Screening (≤ 60 days before Day 1)[1]			Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	50	52	56	60	64	68	72	76	78 (EOT)	UV for a change in AD medication	FU/ET[2]
Study Day	**V1**	**V2**	**V3**	**1**	**29 ± 3**	**57± 3**	**85 ±3**	**113 ±3**	**141 ±3**	**169 ±3**	**183 ±3**	**197 ±3**	**225 ±3**	**253 ±3**	**281 ±3**	**309 ±3**	**337 ±3**	**351 ±3**	**365 ±3**	**393 ±3**	**421 ±3**	**449 ±3**	**477 ±3**	**505 ±3**	**533 ±3**	**547 ±3**		**659 ±7**
Neurological Examination	X						X			X							X							X		X		X
12-lead paper ECG	X									X							X							X		X		X
Vital Signs[8]	X			X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X			X
Hematology, Blood Chemistry and Urinalysis	X			X						X							X							X		X		X
Randomization				X																								
Study Drug Infusion				X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X			
Anti-aducanumab Ab[9]				X						X							X							X		X		X
Aducanumab Concentration[10]				X[11]	X[11]		X[11]	X	X[11]	X[11]		X[11]	X						X[11]	X					X			
Biomarkers (RNA, serum, and plasma)[12]	X									X							X							X		X		X
CSF Collection (optional)	X[13]																									X		
Amyloid PET[14]			X								X															X		
RBANS	X																											
CDR	X										X							X								X	X	X
MMSE	X										X							X								X	X	X
ADCS-ADL-MCI		X[15]									X							X								X	X	X
ADAS-Cog 13		X[15]									X							X								X	X	X

Study Week	Screening (≤ 60 days before Day 1)[1]			Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	50	52	56	60	64	68	72	76	78 (EOT)	UV for a change in AD medication	FU/ET[2]
Study Day	V1	V2	V3	1	29 ±3	57± 3	85 ±3	113 ±3	141 ±3	169 ±3	183 ±3	197 ±3	225 ±3	253 ±3	281 ±3	309 ±3	337 ±3	351 ±3	365 ±3	393 ±3	421 ±3	449 ±3	477 ±3	505 ±3	533 ±3	547 ±3		659 ±7
NPI-10		X 15									X							X								X		X
EQ-5D (SR)		X 16									X							X								X		X
EQ-5D (IR-S)		X 16									X							X								X		X
EQ-5D (IR-I)		X 16									X							X								X		X
mPDQ-20		X 16									X							X								X		X
Caregiver Burden Questionnaire		X 16									X							X								X		X
C-SSRS				X															X							X		X
AE Reporting				Monitor and record continuously throughout the study																								
Concomitant therapy and procedures				Monitor and record continuously throughout the study																								
SAE reporting				Monitor and record continuously throughout the study																								

AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); ApoE = apolipoprotein E; CDR = Clinical Dementia Rating scale; CSF: cerebrospinal fluid ; C-SSRS = Columbia Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) =EQ-5D, subject self-reported; EOT = End of Treatment; ET = Early Termination; FU = Follow-up; HbA1c = glycosylated hemoglobin; HIV = human immunodeficiency virus; MMSE = Mini-Mental State Examination; mPDQ-20 = modified Perceived Deficits Questionnaire-20; MRI = magnetic resonance imaging; NPI-10 = Neuropsychiatric Inventory; PET = positron emission tomography; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; RNA = ribonucleic acid; SAE = serious adverse event; UV = unscheduled visit; V1, V2, V3 = Screening Visit 1, Screening Visit 2 and Screening Visit 3

[1] Examinations required for assessment of subject eligibility must be performed at V1. Brain MRI (Table 2) should only be performed once the subject meets eligibility criteria at V1. Amyloid PET should only be performed if the subject meets eligibility criteria at V1 and V2.

[2] Visit to be completed in cases of early termination or for subjects who do not enroll in the long-term extension.
[3] Subjects may sign this optional form for an initial screening which allows administration of the RBANS, CDR and MMSE only.
[4] All subjects must sign this informed consent, including subjects who have signed the initial screening consent once they have met the RBANS, CDR and MMSE eligibility criteria.
[5] Only for subjects entering the long-term extension.
[6] Can be collected at any point during and after Screening.
[7] Required for women of child bearing potential only (See Section 15.5).
[8] Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes.
[9] Sample collection for anti-aducanumab antibody will be performed prior to blood collection for aducanumab concentration or study drug infusion
[10] Blood sampling for aducanumab concentration will be performed prior to infusion.
[11] One additional blood sample for aducanumab concentration will be collected between 10 and 60 minutes after completion of the infusion and line flush
[12] Sample will be collected prior to infusion (where applicable).
[13] May be collected at any point in time during Screening after eligibility at V1 is confirmed but if collected on the same day as an MRI, it should be collected after the MRI is performed.
[14] Screening PET is required for all subjects, PET at Week 26 and Week 78 will only be conducted in selected sites for subjects who are participating in the PET cohort.
[15] Must be performed within 14 days of V1, but not on the same day as the screening RBANS, CDR or MMSE.
[16] May be performed at any point during screening after the subject has met eligibility criteria on the RBANS, CDR and MMSE.

Table 2: Brain MRI, Aria Management, and Follow-up Phone Call Schedule During the Placebo-Controlled Period

Study Week	Screening[1] (≤ 60 days before Day 1)			Placebo-Controlled Period												Unscheduled Visit for ARIA[2]	FU[3] /ET
				Day 1	2	6	10	14	18	22	26	30	42	54	78		94
Study Day	V1	V2	V3	1	15±3	43±3	71±3	99±3	113±3	155±3	183±3	211±3	295±3	379±3	547±3		826 ±7
Follow-up Phone Call					X	X	X	X	X	X	X	X					
Brain MRI[4]		X						X		X		X	X	X	X	X	X
Aducanumab Concentration[5]										X		X		X			X
MOCA				X												X	

ARIA = amyloid related imaging abnormalities; ET = Early Termination; FU = follow-up; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; V1, V2, V3 = Screening Visit 1, Screening Visit 2, and Screening Visit 3

[1] Brain MRI (V2) will not be performed until the subject has met the eligibility criteria and has acceptable laboratory tests from V1.

[2] Details on ARIA management are in Section 7.2.

[3] Assessments to be completed as part of an ET Visit or for subjects not enrolling into the long-term extension.

[4] Arterial spin labeling MRI and task free functional MRI will be performed only at a subset of sites.

[5] One sample will be collected within 2 days after the MRI visit. Exact collection date and time will be captured for all pharmacokinetic blood samples on a specified case report form.

Table 3: Long-Term Extension Schedule

Study Week	80	84	88	92	96	100	104	108	112	116	120	124	128	132	136	140	144	148	152	156	160	164	168	172	176	180	182 (EoT)	UV for a change in AD medication	FU /ET
Study Day	561 ±5	589 ± 5	617 ± 5	645 ± 5	673 ± 5	701 ± 5	729 ± 5	757 ± 5	785 ± 5	813 ± 5	841 ± 5	869 ± 5	897 ± 5	925 ± 5	953± 5	981± 5	1009 ±5	1037 ±5	1065 ±5	1093 ±5	1121 ± 5	1149 ± 5	1177 ± 5	1205 ± 5	1233 ± 5	1261 ±5	1275± 5		1387±7
Randomization	X[1]																												
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Urine Pregnancy Test[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Physical Examination				X			X						X						X						X		X		X
Neurological Examination				X			X						X						X						X		X		X
12-lead Paper ECG							X						X						X						X				X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hematology, Blood Chemistry and Urinalysis							X						X						X						X				X
Anti-aducanumab Ab[3]	X						X						X						X						X		X		X
Biomarkers (RNA, serum, and plasma)[3]							X						X						X						X				X
Aducanumab Concentration[3]	X						X						X						X						X		X		X
Study Drug Infusion	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
CSF Collection (optional)[4]														X													X		
Amyloid PET[5]														X													X		
CDR [6]							X							X							X						X	X	X
MMSE[6]							X							X							X						X	X	X
ADAS-Cog 13[6]							X							X							X						X	X	X
ADCS-ADL-MCI[6]							X							X							X						X	X	X
NPI-10[6]							X							X							X						X		X

Study Week	80	84	88	92	96	100	104	108	112	116	120	124	128	132	136	140	144	148	152	156	160	164	168	172	176	180	182 (EoT)	UV for a change in AD medication	FU /ET
Study Day	561 ±5	589 ±5	617 ±5	645 ±5	673 ±5	701 ±5	729 ±5	757 ±5	785 ±5	813 ±5	841 ±5	869 ±5	897 ±5	925 ±5	953± 5	981± 5	1009 ±5	1037 ±5	1065 ±5	1093 ±5	1121 ±5	1149 ±5	1177 ±5	1205 ±5	1233 ±5	1261 ±5	1275± 5		1387±7
EQ-5D (IR-S)[6]							X							X							X						X		X
EQ-5D, (IR-I)[6]							X							X							X						X		X
Caregiver Burden Measures[6]							X							X							X						X		X
C-SSRS														X													X		X
AE Reporting	Monitor and record continuously throughout the study																												
Concomitant Therapy and procedures	Monitor and record continuously throughout the study																												
SAE Reporting	Monitor and record continuously throughout the study																												

AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); CDR = Clinical Dementia Rating; CSF: cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) = EQ-5D, subject self-reported; EOT = End of Treatment; ET = Early Termination; FU = Follow-up; LTE = long-term extension; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; PET = positron emission tomography; SAE = serious adverse event; UV = unscheduled visit.

[1] Subjects who were in the placebo group during the placebo-controlled period will be randomized to aducanumab high and low dose (1:1 ratio).
[2] Required for women of childbearing potential only (Section 15.5).
[3] Sample will be collected prior to infusion (where applicable).
[4] Enrolled subjects who consented to CSF collection during the placebo-controlled period will have the option to consent to CSF collection during the LTE.
[5] Only for subjects who participate in the PET cohort.
[6] To be performed 14 ±7 days after the indicated dosing visit (i.e., Weeks 106, 134 and 162) and at Week 182.

Table 4: Brain MRI, Aria Management, and Follow-Up Phone Call Schedule During the Long-Term Extension

	Long-Term Extension													FU/ET
Study Week	**82**	**86**	**90**	**94**	**98**	**102**	**106**	**110**	**122**	**134**	**158**	**182**	**Unscheduled visit for ARIA[1]**	**198**
Study Day	**575±5**	**603±5**	**631±3**	**659±5**	**687±5**	**715±5**	**743±5**	**771±5**	**855±5**	**937±5**	**1107±5**	**1247±5**		**1387 ±7**
Follow-up Phone Call	X	X	X	X	X	X	X	X						
Brain MRI[2]				X		X		X	X	X	X	X	X	X
MOCA													X	

ARIA = amyloid related imaging abnormalities; ET = Early Termination; FU = follow-up; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging

[1] Details on ARIA management are in Section 7.2.

[2] Arterial-spin labeling MRI and task-free functional MRI will be performed only at a subset of sites.

4.3. Additional Information

4.3.1. Site Personnel

For each subject, the Principal Investigator (PI) of the site will designate the following investigational site personnel:

- Two independent rating health care professionals (the PI cannot serve as a rating health care professional); one who is responsible for administering the Clinical Dementia Rating (CDR) and a second who will administer the Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13], Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) (ADCS-ADL-MCI), and the Mini-Mental State Examination (MMSE)

  The rating health care professionals must not be involved with any other aspect of subject care and management and must remain blinded to adverse events (AEs), concomitant therapy, laboratory data, imaging data or any other data that have the potential of revealing the treatment assignment.

  To ensure consistency across sites, rating health care professionals must complete the standardized study-specific qualification process on clinical efficacy assessment scoring prior to administration of the specific assessment at their site. All sites should attempt to maintain the same rating health care professional throughout the study for specific assessments. Each subject should have the same rating health care professional perform the subject's specific rating assessment throughout the study. If a rating health care professional has to be replaced, the new rating health care professional must undergo the study-specific qualification process prior to administration of the assessment.

- A treating health care professional (the PI may serve as a treating health care professional) who is responsible for the following:
  - Administration of Montreal Cognitive Assessment (MOCA) at Day 1 and during management of ARIA cases.
  - Management of the routine neurological care of the subject.
  - Assessment (including assignment of causality) and treatment of AEs.
  - Review of selected hematology and blood chemistry results from the central laboratory to assess if the subject's study treatment should be temporarily withheld or permanently discontinued according to the criteria detailed in Section 10.1.

  Hematology and blood chemistry data will be sent to the investigational sites to aid in management of the subject. As with other laboratory and clinical information, these data should NOT be reviewed by the rating health care professionals.

The roles of independent raters and treating health care professional are NOT interchangeable at the subject level. In addition, the 2 independent raters are not interchangeable at the subject

level. If a rater has administered the CDR to a subject they may not administer the other neurocognitive assessments to that subject at any point during the study.

- An unblinded pharmacist (or authorized designee) will be responsible for the storage, distribution, preparation and accountability of study treatment. The unblinded pharmacist will also be responsible for maintaining the unblinded pharmacy record separate from the main study file in order to support the study blind.

5. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 50% to 75% of all cases. Alzheimer's Disease International estimates that as of 2013, there were 44.4 million people living with dementia worldwide and that this figure will increase to 135.5 million by 2050 [Alzheimer's Disease International 2014].

Clinically, AD is a progressive neurodegenerative disorder characterized by an insidious and unrelenting decline in cognition and behavioral disturbances that result in the person's inability to perform usual activities of daily living [Jack 2013].

Pathologically, AD is defined by the presence in the brain of extracellular neuritic plaques containing β-amyloid (Aβ) peptide and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau proteins. The pathogenesis of these plaques and tangles and how they contribute to the clinical syndrome remain to be fully elucidated, but the leading hypothesis — the "amyloid cascade"— proposes that the driving force behind the disease process is the accumulation of Aβ resulting from an imbalance between Aβ production and Aβ clearance in the brain [Hardy and Selkoe 2002].

The current view of AD, the disease process and its clinical manifestations, is that it manifests along a continuum rather than having categorical stages. Evidence suggests the pathophysiological changes begin years before clinical onset and as the disease progresses cognitive impairments, behavioral changes, and functional disability manifest [Jack 2013]. Revised criteria for the clinical diagnosis of AD were published by the National Institute on Aging (NIA) and the Alzheimer's Association (AA) [Albert 2011; McKhann 2011; Sperling 2011] and the International Working Group (IWG) [Dubois 2010; Dubois 2014], and a group that included members from both NIA-AA and IWG published recommendations to harmonize the criteria [Morris 2014]. These criteria base the diagnosis of AD on both clinical and biological elements, recognizing the existence of a nonclinical stage of the disease by accepting AD diagnoses prior to signs of dementia using AD biomarkers.

The scientific community has shifted its focus to target patients in the earlier course of the disease continuum with the belief that those patients are more likely to benefit from anti-amyloid therapy. Supporting this hypothesis are results from solanezumab and crenezumab studies that have shown a trend in slowing cognitive decline in mild but not moderate AD [Doody 2014; Fagan 2014].

There are currently no therapies that modify the course of AD, but several potential disease-modifying drug candidates are under investigation. These candidates include small molecules and immunotherapy (active and passive) that target the Aβ pathway and aim to provide therapeutic benefit by reducing either soluble or insoluble forms of Aβ in the brain and cerebrospinal fluid (CSF). Aducanumab is a human monoclonal antibody that recognizes aggregated forms of Aβ, including soluble Aβ oligomers and deposited fibrillar Aβ. Earlier publications have reported on results that demonstrated in the brain of an animal model of AD that both soluble oligomers and amyloid plaques are neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008] and clearance of amyloid plaques could lead to normalization of

calcium homeostasis and neuronal activity, as well as reduction of oxidative stress [Rozkalne 2009; Spires-Jones 2009]. Similarly, patients with AD who generated anti-Aβ antibodies after active immunization with aggregated Aβ(42) showed slower rates of decline of cognitive function and activities of daily living [Hock 2003].

5.1. Profile of Previous Experience with Aducanumab

5.1.1. Nonclinical Experience

Aducanumab is a unique human, anti-Aβ monoclonal antibody identified and derived from B lymphocytes using the reverse translational medicine approach. Using this technique, immune repertoires obtained from cohorts of healthy elderly human donors with excellent cognitive performance or with impaired but stable courses were screened for memory B cells against aggregated Aβ.

In vitro studies have demonstrated that aducanumab and its analogs are highly selective for soluble oligomeric and insoluble fibrillar forms of Aβ relative to soluble low-molecular-weight forms of Aβ. In vivo pharmacology studies indicated that a murine immunoglobulin (Ig) G2a chimeric version of the antibody (ch12F6A) with similar properties significantly reduced amyloid plaque burden in the brains of aged Tg2576 mice, a mouse model of AD, through a microglia-mediated phagocytic mechanism. These data suggest aducanumab could provide benefit by reducing plaque burden.

The toxicokinetic profile of aducanumab was evaluated in Tg2576 mice in 13-week and 6-month studies and in cynomolgus monkeys in a 4-week study. Of the 2 species, the Tg2576 mouse is considered the primary pharmacologically relevant species given that these mice accumulate amyloid plaques in the cerebral parenchyma and vasculature. In addition to the standard histopathological evaluation in mice, Perls' staining of hemosiderin (a breakdown product of hemoglobin) was performed to quantify microhemorrhage. Microhemorrhage has been observed both as a background finding in transgenic mouse models of AD [Winkler 2001], including Tg2576 mice [Kumar-Singh 2005], and as a drug-related finding in transgenic mice treated with some anti-Aβ antibodies [Pfeifer 2002; Racke 2005; Wilcock and Colton 2009].

Findings consistent with amyloid plaques and vascular amyloid were identified in the brain sections of animals in all groups, including the control group, as expected with this model. In both studies, repeated administration of ch12F6A or aducanumab was well tolerated with no treatment-related deaths observed during the dosing period. In the 13-week toxicology study, meningeal/cerebral vascular inflammation and/or vascular thickening were observed in mice dosed with ch12F6A ≥70 mg/ kg compared with the control group. In the 6-month study, although slight differences were observed between ch12F6A-treated groups and the control group, animals treated with aducanumab were comparable to the control animals. The evaluation of microhemorrhage, characterized by quantification of hemosiderin in Perls stained brain sections of each main study and recovery animal, demonstrated no significant increase in scores with ch12F6A or aducanumab treatment in either study. The incidence and severity of hemorrhage or cerebral vascular inflammation were comparable in the 13-week and 6-month mouse studies.

See the Investigator's Brochure (IB) for detailed information on nonclinical studies.

5.1.2. Clinical Experience

Aducanumab has been evaluated in one completed single ascending dose study (221AD101) and one ongoing multiple ascending dose study (221AD103):

- Study 221AD101 was a Phase 1, randomized, double-blind, placebo-controlled, study of aducanumab in subjects with mild or moderate AD.

  The primary objective was to evaluate the safety and tolerability of a range of aducanumab doses (0.3 to 60 mg/kg) when administered as single intravenous (IV) infusions. The secondary objectives were to assess the pharmacokinetic (PK) and immunogenicity of aducanumab after single-dose administration.

  A single dose of aducanumab up to 30 mg/kg was demonstrated to be well tolerated. Dose-limiting ARIA (2 subjects with ARIA-E [edema] and 1 subject with ARIA-E and ARIA-H [microhemorrhage]) was observed in the 60 mg/kg dose group resulting in termination of further dosing in that cohort; no cases of ARIA were observed at single doses below 60 mg/kg. The PK profile was dose linear.

- Study 221AD103 is a randomized, double-blind, placebo-controlled multiple dose study of aducanumab in subjects with prodromal or mild AD who are amyloid positive. The study comprises a placebo-controlled period with subjects receiving monthly doses of aducanumab (fixed doses of 1, 3, 6, or 10 mg/kg, or titration up to 6 mg/kg) or placebo for a year followed by a dose-blind long-term extension (LTE) period with subjects receiving monthly doses of aducanumab.

  The primary objective of the study is to evaluate the safety and tolerability of multiple doses of aducanumab administered monthly as single IV infusions. The secondary objectives are to assess the effect of aducanumab on cerebral amyloid plaque content as measured by ^{18}F-florbetapir positron emission tomography (PET), and to evaluate the PK and immunogenicity of aducanumab after multiple-dose administration. Exploratory objectives include assessment of the effect of aducanumab on the clinical progression of AD as measured by CDR- sum of boxes (SB) and MMSE.

  To date, ARIA has been the most frequent AE reported in the study. ARIA-E was radiographically monitored by magnetic resonance imaging (MRI) and typically observed early in treatment (between 2 to 5 doses). In most cases, ARIA-E resolved 4 to 12 weeks after onset and ARIA-H was typically stable 2 to 4 weeks after onset. Incidence of ARIA has been observed to be both dose and Apolipoprotein E4 (ApoE ε4) carriage-dependent, especially at the highest doses (refer to the IB for details on events of ARIA).

  Protocol-defined interim analyses have demonstrated a dose- and time-dependent reduction of brain amyloid burden after 6 months of dosing (Week 26), with statistical significance achieved in the 3, 6, and 10 mg/kg groups compared with placebo, and after 1 year of dosing (Week 54), with statistical significance achieved in the 3 and 10 mg/kg groups compared with placebo (6 mg/kg data not yet

available). The results demonstrate target engagement (amyloid plaques) and a pharmacodynamic effect (dose-dependent amyloid reduction). In addition results from the interim analyses showed an effect at 1 year on the exploratory endpoints CDR-SB and MMSE, suggesting a reduction in the progression of clinical impairment for aducanumab-treated versus placebo-treated subjects. At Week 54, adjusted mean change (increase) from baseline in CDR-SB score was smaller for both the 3 and 10 mg/kg groups compared with placebo, with statistical significance achieved in the 10 mg/kg group (6 mg/kg data not yet available). At Week 52, adjusted mean changes (decreases) in MMSE score from baseline were statistically significant in the 3 and 10 mg/kg groups (Week 54 6 mg/kg data not yet available). Refer to the IB for details on interim analyses results.

5.2. Study Rationale

The purpose of this study is to assess the efficacy and safety of aducanumab compared with placebo in subjects with early AD including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD. Aducanumab is a human monoclonal antibody that recognizes aggregated forms of Aβ, including soluble Aβ oligomers and deposited fibrillar Aβ. Earlier publications have demonstrated that both soluble oligomers and amyloid plaques are neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008] and clearance of amyloid plaques could lead to normalization of calcium homeostasis and neuronal activity, as well as reduction of oxidative stress in the brain of an animal model of AD [Rozkalne 2009; Spires-Jones 2009]. For this reason, treatment with aducanumab is expected to slow progression of AD, while preserving global function longer, when compared with untreated subjects.

Interim analyses of the ongoing multiple dose study (Study 221AD103) have demonstrated target engagement, a PD effect on amyloid reduction, and an effect on CDR-SB and MMSE suggestive of a reduction in the progression of clinical impairment for aducanumab-treated subjects. These results along with the observed safety and tolerability profile warrant the further Phase 3 investigation of aducanumab in a patient population spanning the early stages of the AD continuum.

5.3. Rationale for Dose and Schedule Selection

The dosing regimen selected for this study was based on the PK and PD relationship for removal of brain amyloid and effect on CDR-SB and MMSE observed in Study 221AD103 interim analyses and on safety, tolerability, and PK data from studies 221AD101 (complete) and 221AD103 (ongoing).

The dose- and time-dependent reduction of brain amyloid burden observed with aducanumab treatment was statistically significant at doses of 3, 6 and 10 mg/kg after 6 months of dosing and at 3 and 10 mg/kg after 12 months of dosing (6 mg/kg data not yet available). The effect on mean decrease from baseline in CDR-SB after 12 months of dosing was observed at both 3 and 10 mg/kg (6 mg/kg data not yet available), with statistical significance achieved at 10 mg/kg. The effect on mean decrease from baseline in MMSE score was statistically significant at 3 and 10 mg/kg. These data indicate that 3 mg/kg could be considered an acceptable dose for Phase 3

studies; however, given the dose-dependent nature of these observations, the use of higher doses (6 and 10 mg/kg) could offer greater benefit at acceptable risk.

ARIA has been identified as an event that may occur with anti-amyloid targeting drug candidates and is considered an event of special interest in the aducanumab program. To date, the incidence of ARIA has been observed to be both dose and ApoE ε4 carriage dependent, especially at the highest doses. In an effort to maximize the dose-dependent amyloid reduction and effect on CDR-SB and MMSE that have been observed with doses of 3 mg/kg and higher while maintaining ARIA incidence, severity, and related discontinuation rate within acceptable levels, a titration regimen will be explored. It has been suggested that the ARIA observed following treatment with amyloid targeting agents may be due, in part, to the initial large removal of amyloid and subsequent saturation of perivascular brain amyloid clearance mechanisms [Weller 2008]. Slow titration to the target dose is expected to result in slower initial amyloid removal, yet trigger alternative mechanisms of amyloid clearance including monoclonal antibody-dependent Fc-mediated microglial clearance [Ostrowitzki 2012] which would prevent saturation of amyloid clearance and subsequent ARIA during titration and once the target dose is reached. Since aducanumab-induced ARIA has been demonstrated to occur early during treatment, with most cases occurring within the first 5 doses, titration of aducanumab for up to 6 doses prior to reaching the target dose may result in reduction of ARIA incidence and severity.

Given the tolerability and apparent efficacy of aducanumab shown to date, the doses to be tested using a titration regimen are 3 and 6 mg/kg for ApoE ε4 carriers, and 6 and 10 mg/kg for ApoE ε4 non-carriers. Titration will start at 1 mg/kg and will escalate to 3, 6 and 10 mg/kg as detailed below.

5.3.1. Dosing Scheme

5.3.1.1. Placebo-Controlled Period

Doses will be administered approximately 4 weeks apart, over approximately 76 weeks (a total of 20 doses). Based upon their ApoE ε4 carrier status, subjects will be assigned to 1 of 3 treatment groups (450 subjects each) in a 1:1:1 ratio (aducanumab low dose: aducanumab high dose: placebo) as follows (Table 5 and Figure 1):

ApoE ε4 carrier

- Low dose (3 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg thereafter
- High dose (6 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 4 doses, and 6 mg/kg thereafter
- Placebo

  Saline infusion

ApoE ε4 non-carrier

- Low dose (6 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 4 doses, and 6 mg/kg thereafter

- High dose (10 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter

- Placebo

  Saline infusion

Table 5: Dosing Scheme for Aducanumab by Regimen

Dose (Month)		**1**	**2**	**3**	**4**	**5**	**6**	**7 to 20**
Regimen		**Dose (mg/kg)**						
ApoE ε4 (+)	**Low Dose**	1	1	3	3	3	3	3
	High Dose	1	1	3	3	3	3	6
	Placebo	saline						
ApoE ε4 (-)	**Low Dose**	1	1	3	3	3	3	6
	High Dose	1	1	3	3	6	6	10
	Placebo	saline						

5.3.2. Dosing Scheme Modification

An independent data monitoring committee (IDMC) will review unblinded safety data, including serious AEs (SAEs) and incident cases of ARIA, from all ongoing aducanumab studies (e.g., Studies 221AD103, 221AD104, 221AD301, and 221AD302) as described in the IDMC charter.

The dosing scheme can be modified in the following circumstances:

- Safety and tolerability of the high dose

  If any of the high doses proposed (10 mg/kg in ApoE ε4 non-carriers and 6 mg/kg in ApoE ε4 carriers) is deemed not acceptable, enrollment for the high dose group(s) will be terminated and subjects will not be replaced. Subjects who have already been randomized to the discontinued dose will be down-dosed to the next available dose according to their ApoE ε4 carrier status. Definition of low and high dose regimens will be revised as described in Section 16.

- Benefit of titration

  A titration schedule has been implemented in this Phase 3 study and in the ongoing multiple-dose Study 221AD103. If, based upon review of the data from

Study 221AD103, titration is not deemed beneficial, it will be eliminated, and subsequently enrolled subjects who are ApoE ε4 carriers will receive a fixed dose of 3 or 6 mg/kg and non-carriers will receive 6 or 10 mg/kg.

5.3.3. Long-Term Extension

Subjects who received aducanumab in the placebo-controlled period and who enter the LTE will continue to receive the same dose of aducanumab that they were on at the end of the placebo-controlled period. Subjects who receive placebo during the placebo-controlled period and who enter the LTE period will be assigned to 1 of 2 treatment groups, based upon their ApoE ε4 carrier status, in a 1:1 ratio (aducanumab low dose: aducanumab high dose). Subjects will be dosed using the same regimen described for the placebo-controlled period (see Table 5 and Figure 1).

Any modifications to the dosing scheme (i.e. termination of high dose groups and replacement of titration with fixed dosing, as described in Section 5.3.2) will also be implemented in the LTE.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

The primary objective of the study is to evaluate the efficacy of monthly doses of aducanumab in slowing cognitive and functional impairment as measured by changes in the CDR-SB score as compared with placebo in subjects with early AD.

The primary endpoint that relates to this objective is change from baseline in CDR-SB score at Week 78.

6.2. Secondary Objectives and Endpoints

A secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by the MMSE.

- The endpoint that relates to this objective is change from baseline in MMSE score at Week 78.

Another secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by ADAS-Cog 13.

- The endpoint that relates to this objective is change from baseline in ADAS-Cog 13 score at Week 78.

Another secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by ADCS-ADL-MCI.

- The endpoint that relates to this objective is change from baseline in ADCS-ADL-MCI score at Week 78.

6.3. Tertiary Objectives and Endpoints

6.3.1. Tertiary Objectives

Safety and Tolerability

- To assess the safety and tolerability of monthly doses of aducanumab.
- To assess the immunogenicity of aducanumab.

Biomarker

- To assess the effect of aducanumab on cerebral amyloid plaque content as measured by amyloid PET imaging (in a subset of approximately 400 subjects).
- To assess the effect of aducanumab on various morphometric measures in certain brain areas as measured by MRI.
- To assess the effect of aducanumab on functional connectivity by task free functional (tf)-fMRI (where available).

- To assess the effect of aducanumab on cerebral blood flow by arterial spin labeling (ASL)-MRI (where available).
- To assess the effect of aducanumab on disease-related biomarkers in CSF which will include, but are not limited to, amyloid and tau proteins (in a subset of subjects).
- To assess the effect of aducanumab on disease-related biomarkers in blood which may include, but are not limited to, amyloid and tau proteins.

Efficacy

- To assess the effect of aducanumab on behavior as measured by the Neuropsychiatric Inventory (NPI-10).
- To assess the effect of aducanumab on patient health status, measured by EuroQol health status measures (EQ-5D [informant-rated and patient self-reported]).
- To assess the effect of aducanumab on the informant/study partner's own health status, measured by the EQ-5D.
- To assess the effect of aducanumab on patient self-reported cognitive function, measured by the modified Perceived Deficits Questionnaire-20 (mPDQ-20) [Lenderking 2014].
- To assess the effect of aducanumab on caregiver burden measures.
- To assess the correlation between primary endpoints and key biomarker endpoints.

Pharmacokinetics

- To explore the potential relationships between PK or exposure and response (e.g., clinical and biomarker endpoints) including covariate analysis.
- To explore the potential effect of co-medications on the PK of aducanumab using population PK.

6.3.2. Tertiary Endpoints

Safety and Tolerability:

- Incidence of all AEs and SAEs.
- Brain MRI findings including incidence of ARIA-E and ARIA-H.
- Clinical laboratory shifts in reported values.
- Clinically significant changes in vital sign measurements and electrocardiograms (ECGs).
- Incidence of anti-aducanumab antibodies in serum.

Biomarkers:

- Change from baseline in amyloid PET signal at Week 26 (in a subset of subjects).

- Change from baseline in amyloid PET signal at Week 78 (in a subset of subjects).
- Change from baseline in whole brain volume, hippocampal volume, ventricular volume, and cortical gray matter volume measured by MRI over time.
- Change from baseline in functional connectivity as measured by tf-fMRI (where available) over time.
- Change from baseline in cerebral blood flow as measured by ASL-MRI (where available) over time.
- Change in disease-related biomarker levels in CSF, which will include, but are not limited to, amyloid or tau proteins at Week 78 (in a subset of subjects).
- Change in disease-related biomarker levels in blood, which may include, but are not limited to, amyloid or tau proteins at Week 24.
- Change in disease-related biomarker levels in blood, which may include, but are not limited to, amyloid or tau proteins at Week 78.

Efficacy

- Change from baseline in NPI-10 score at Week 78.
- Change from baseline in subject-self-reported EQ-5D index score at Week 78.
- Change from baseline in informant-rated subject EQ-5D index score at Week 78.
- Change from baseline in informant/care partner’s own EQ-5D index-score at Week 78.
- Change from baseline in mPDQ-20 at Week 78.
- Changes in caregiver burden questionnaire over time.
- Correlation between clinical and biomarker endpoints over time.

Pharmacokinetics

- Serum concentrations of aducanumab, population PK parameters of aducanumab including but not limited to clearance and volumes of central and peripheral compartments.

6.4. Long Term Extension Objectives and Endpoints

6.4.1. Objectives

- To evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD.
- To evaluate the long-term efficacy of aducanumab treatment as measured by clinical, radiological, and additional assessments reported by the subject and informant/care partner.

6.4.2. Endpoints

- The incidence of AEs and/SAEs; brain MRI findings (including the incidence of ARIA-E and ARIA-H); and the incidence of anti-aducanumab antibodies in serum over the placebo-controlled and LTE periods of the study.
- Change in the following measures over the placebo-controlled and LTE periods of the study:
  - CDR-SB score.
  - MMSE score.
  - ADAS-Cog 13 score.
  - ADCS-ADL-MCI score.
  - Amyloid PET signal (in a subset of subjects).
  - Whole brain volume, hippocampal volume, ventricular volume, and cortical gray matter volume measured by MRI.
  - Functional connectivity as measured by tf-fMRI (where available).
  - Cerebral blood flow as measured by ASL-MRI (where available).
  - Disease-related biomarker levels in CSF which will include, but are not limited to, amyloid and tau proteins (in a subset of subjects).
  - Disease-related biomarker levels in blood which may include, but are not limited to, amyloid and tau proteins.
  - NPI-10 total score.
  - Informant-rated EQ-5D index score.
  - Informant/care partner’s own self-reported EQ-5D index score.
  - Caregiver burden measures.

7. STUDY DESIGN

7.1. Study Overview

Study 221AD302 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects with early AD, including MCI due to AD and a subset of mild AD, followed by an optional 24-month dose-blind LTE study. Approximately 1350 subjects will be enrolled across approximately 150 centers globally. The primary study objective is to evaluate the efficacy of monthly doses of aducanumab on the CDR-SB relative to placebo. Secondary objectives include assessment of the effect of monthly doses of aducanumab on clinical progression as compared to placebo. The safety of monthly doses of aducanumab will also be evaluated.

Subjects will receive infusions of aducanumab or placebo approximately every 4 weeks for approximately 18 months (a total of 20 doses). Subjects will be randomized to receive aducanumab low dose : aducanumab high dose : placebo in a 1:1:1 ratio. The randomization will be stratified by site and ApoE ε4 status (carrier or non-carrier). Subject enrollment will be monitored so that approximately 60% to 70% ApoE ε4 carriers are enrolled. Enrollment will also be monitored, via interactive response technology (IRT), such that subjects with mild AD represent a small percentage of the total enrolled in the trial.

At the end of the double-blind, placebo-controlled treatment period, subjects who meet the extension entry criteria may enter a 24-month long-term safety and efficacy extension period, with all subjects receiving aducanumab approximately every 4 weeks (a total of 26 doses).

The total duration of study participation for each subject only participating in the placebo-controlled period of the study will be up to approximately 102 weeks, including a series of screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, and a safety follow-up period of approximately 18 weeks after the final dose. The total duration of study participation for each subject participating in the placebo-controlled period and the LTE will be up to approximately 206 weeks, including a series of screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, a 4-week follow-up period, a 100-week aducanumab dose-blind treatment period, and a safety follow-up period of approximately 18 weeks after the final dose. The follow-up period of 18 weeks is based on an estimated mean elimination half-life in humans of 16 to 24 days (mean approximately 20 days, based on results from the single ascending dose study [Study 221AD101]) and anticipated brain concentrations of aducanumab of less than one-third the EC_{50} (inhibitory concentration at 50% of the maximum observed biologic effect) for binding fibrillar amyloid at 8 weeks after the last dose.

During the placebo-controlled period, ApoE ε4 carriers will receive placebo, aducanumab 3 mg/kg, or aducanumab 6 mg/kg whereas ApoE ε4 non-carriers will receive placebo, aducanumab 6 mg/kg, or aducanumab 10 mg/kg. Aducanumab will be titrated for up to 6 doses prior to reaching the target dose as shown in Table 5 and Figure 1. Subjects who received aducanumab in the placebo-controlled period and who enter the LTE period will receive the

same dose of aducanumab that they received at the end of the placebo-controlled period (up to 6 mg/kg and 10 mg/kg in ApoE ε4 carriers and non-carriers, respectively). Subjects who received placebo during the placebo-controlled period and who enter the LTE period will be assigned to treatment based upon their ApoE ε4 carrier status in a 1:1 ratio (aducanumab low dose: aducanumab high dose); aducanumab will be titrated for up to 6 doses prior to reaching the target dose following the same schedule described for the placebo-controlled period.

See Section 5.3.2 for details of dosing scheme modification.

Individual dose adjustments may also be implemented to subjects who develop ARIA. See Section 7.2.1.

Investigators, study site staff (except for the designated unblinded pharmacist/technician), and study subjects will be blinded to the subjects' randomized treatment assignment for the placebo-controlled period. During the LTE, investigators and subjects will remain blinded to the treatment assignment in the placebo-controlled period and the aducanumab dose for the LTE.

7.2. Study Specifics

7.2.1. Dose Suspension, Modification or Termination for ARIA Events

Discontinuation of Dosing for a Given Subject

The central MRI reading center will report incident cases of ARIA-E and ARIA-H to both the Sponsor and the Principal Investigator within a specified time after observing the finding on MRI per the imaging manual procedures. All cases of ARIA will be reviewed by the Sponsor and the Principal Investigator; decisions on dosing continuation, interruption, or discontinuation will be based on clinical symptoms, and the MRI information provided by the central reader. IDMC notification rules will be outlined in the IDMC charter. Disposition of ARIA-E cases is presented in Table 6 , ARIA-H (microhemorrhage) in Table 7, and ARIA-H (superficial siderosis) in Table 8.

7.2.1.1. Disposition of ARIA-E cases

Table 6: Disposition of ARIA-E Cases

<table>
<tr><th rowspan="2">Clinical Symptom Severity</th><th colspan="3">ARIA-E Severity on MRI</th></tr>
<tr><th>Mild</th><th>Moderate</th><th>Severe</th></tr>
<tr><td>Asymptomatic</td><td>Continue dosing at current dose and schedule</td><td>Suspend dosing; once ARIA-E resolves the subject may resume dosing at next lower dose</td><td>Suspend dosing; once ARIA-E resolves, the subject may resume dosing at next lower dose</td></tr>
<tr><td>Mild</td><td colspan="3" rowspan="2">Suspend dosing; once ARIA-E and clinical symptoms resolve, the subject may resume dosing at next lower dose</td></tr>
<tr><td>Moderate</td></tr>
<tr><td>Severe or Serious</td><td colspan="3">Discontinue Dosing</td></tr>
</table>

- Subjects who develop **mild ARIA-E, per central MRI reading, with no clinical symptoms** at any time during the study may continue in the study at their current

dose. Subjects should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. The Sponsor may require that the subjects discontinue dosing or continue dosing at a lower dose level based on review of safety and MRI data.

- Subjects who develop **moderate or severe ARIA-E, per central MRI reading, with no clinical symptoms** at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. If the ARIA-E has resolved and the subjects remain asymptomati**c**, the subjects may resume treatment but at the next lower dose level. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment. Guidance for dose reduction is presented in Section 7.2.1.4.
- Subjects who develop **mild, moderate, or severe ARIA-E, as per central MRI reading, accompanied by mild or moderate clinical symptoms** at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. If the ARIA-E has resolved and the clinical symptoms have resolved, the subject may resume treatment but at the next lower dose level. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment. Guidance for dose reduction is presented in Section 7.2.1.4.
- Subjects who develop **mild, moderate, or severe ARIA-E, as per central MRI reading, accompanied by severe or serious clinical symptoms** at any time during the study will permanently discontinue treatment. Subjects should complete all scheduled clinic visits for assessments and in addition, have an unscheduled visit for an MRI and MOCA approximately every 4 weeks until the ARIA-E has resolved per centrally read MRI.

7.2.1.2. Disposition of ARIA-H cases

Table 7: Disposition of ARIA-H (microhemorrhage) Cases

<table>
<tr><th rowspan="2">Clinical Symptom Severity</th><th colspan="3">New Incident Microhemorrhages Within 12 Weeks</th></tr>
<tr><th>≥ 1 and ≤ 4</th><th>≥ 5 and ≤ 9</th><th>≥ 10</th></tr>
<tr><td>Asymptomatic</td><td>Continue dosing at current dose and schedule</td><td>Suspend dosing; once ARIA-H is stable the subject may resume dosing at next lower dose</td><td rowspan="4">Discontinue dosing</td></tr>
<tr><td>Mild</td><td colspan="2" rowspan="2">Suspend dosing; once ARIA-H stabilizes and clinical symptoms resolve, the subject may resume dosing at next lower dose</td></tr>
<tr><td>Moderate</td></tr>
<tr><td>Severe or Serious</td><td colspan="2">Discontinue dosing</td></tr>
</table>

7.2.1.2.1. Asymptomatic ARIA-H (microhemorrhage):

- Subjects who develop a **≥ 1 and ≤ 4 new incident microhemorrhage(s)** within 12 weeks at any time during the study may continue treatment at the current dose.
- Subjects who develop **≥ 5 and ≤ 9 new incident microhemorrhages** occurring within 12 weeks at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 2 weeks until the microhemorrhage is confirmed as stable per the centrally read MRI. A microhemorrhage is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks later. Once the microhemorrhage is deemed stable, subjects may resume treatment at the next lower dose. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment. Guidance for dose reduction is presented in Section 7.2.1.4.

Table 8: Disposition of ARIA-H (superficial siderosis) Cases

Clinical Symptom Severity	New Incident Areas of Superficial Siderosis Within 12 Weeks		
	1	2	> 2
Asymptomatic	Continue dosing at current dose and schedule	Suspend dosing; once ARIA-H is stable the subject may resume dosing at next lower dose	Discontinue dosing
Mild	Suspend dosing; once ARIA-H stabilizes and clinical symptoms resolve, the subject may resume dosing at next lower dose		
Moderate			
Severe or Serious	Discontinue dosing		

7.2.1.2.2. Asymptomatic ARIA-H (superficial siderosis):

- Subjects who develop a **single incident focal area of hemosiderosis** (**also referred to as superficial siderosis)** may continue treatment at the current dose, but must have an unscheduled visit for an MRI and MOCA approximately every 2 weeks until the superficial siderosis is confirmed as stable per the centrally read MRI. Superficial siderosis is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks later.
- Subjects who develop **2 focal areas of hemosiderosis (superficial siderosis)** occurring within 12 weeks at any time during the study will temporarily suspend treatment but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 2 weeks until the ARIA-H (superficial siderosis) is confirmed as stable per the centrally read MRI. Superficial siderosis is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks later. Once the superficial siderosis is deemed stable, the subjects may resume treatment at the next lower dose. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment. Guidance for dose reduction is presented in Section 7.2.1.4.

7.2.1.2.3. Symptomatic ARIA-H (microhemorrhage(s) or superficial siderosis):

- Subjects who develop **≤ 9 new incident microhemorrhages or ≤ 2 new focal area of superficial siderosis** within 12 weeks and mild or moderate clinical symptoms will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 2 weeks until the ARIA-H (microhemorrhage(s)) is confirmed as stable per the centrally read MRI. Microhemorrhage(s) are considered stable if they are unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks later. Once the ARIA-H is deemed stable and the clinical symptoms have resolved, the subjects may resume treatment but at the next lower dose level. Only subjects who have not missed more than 4 consecutive doses

will be allowed to resume treatment. Guidance for dose reduction is presented in Section 7.2.1.4.

- Subjects who experience **severe clinical symptoms associated with ARIA-H (microhemorrhage(s) or superficial siderosis)** will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and in addition, have an unscheduled visit for an MRI and MOCA approximately every 2 weeks until the ARIA-H microhemorrhage(s) or superficial siderosis is confirmed as stable per centrally read MRI.

7.2.1.2.4. ARIA-H (microhemorrhage(s) or superficial siderosis) requiring permanent discontinuation:

- Subjects who develop **≥ 10 new incident microhemorrhages or > 2 new focal areas of superficial siderosis** within 12 weeks regardless of clinical severity will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 2 weeks until the ARIA-H microhemorrhage(s) or superficial siderosis is confirmed as stable per central read MRI.

7.2.1.3. Disposition of Coincident ARIA-H and ARIA-E Cases:

Subjects who develop ARIA-H coincident with ARIA-E at any time during the study will follow ARIA-E guidelines. Prior to resuming treatment, where applicable, ARIA-E must resolve, ARIA-H be deemed stable, and the subject must be asymptomatic.

7.2.1.4. Dose Reduction for Subjects Developing ARIA:

Dose reduction guidance is presented in the Table 9 below. If further dose reduction is needed, the next lower dose level will be used. If more than 2 dose reductions are needed, Sponsor approval will be required prior to treatment continuation.

Table 9: Dose Reduction for Subjects Experiencing ARIA, Who Resume Treatment After Suspension

Current Dose	Resuming Dose
10 mg/kg	6 mg/kg
6 mg/kg	3 mg/kg
3 mg/kg	1 mg/kg
1 mg/kg	Placebo
Placebo	Placebo

ARIA = amyloid related imaging abnormality
Current dose refers to the dose that the subject was receiving before ARIA was detected

Subjects who develop ARIA during the placebo-controlled period but continue or resume treatment at an active dose are eligible to enter the LTE and will receive the lowest dose that they

have tolerated during the placebo-controlled period. A subject who is switched to placebo but remains in the study may be titrated to aducanumab 1 mg/kg during the LTE.

7.2.2. Infusion Interruption

If any mild or moderate infusion-related reactions (e.g., headache, chills/rigors, and nausea/vomiting) occur during an infusion, the infusion should be slowed or interrupted and supportive treatment should be instituted at the discretion of the Investigator. After resolution of symptoms, if the infusion had been slowed, the original infusion rate may be resumed; if the infusion had been interrupted, the infusion may be restarted at a rate that does not exceed the original infusion rate. An infusion must be discontinued if not completed within 3 hours.

Refer to the Directions for Handling and Administration [DHA] for infusion rate information.

If a severe infusion-related reaction occurs during an infusion, or an allergic reaction such as urticaria or anaphylaxis occurs, the subject should be discontinued from study treatment but may remain in the study. The subject must be appropriately treated in accordance with local practice.

Severity of events is described in Section 15.2.3.

7.3. Overall Study Duration and Follow-Up

The study period will consist of screening, treatment, and follow-up.

The double-blind, placebo-controlled period of the study will consist of an 8-week screening period, a 76-week treatment period, and a safety follow-up period of 18 weeks after the final dose.

Subjects will have approximately 33 scheduled clinic visits during the placebo-controlled period, and up to 8 telephone safety follow-up contacts, as follows:

- Screening Visits no more than 60 days before the first dose of study treatment on Day 1 (visits will be conducted on multiple days).
- 20 outpatient dosing visits.
- 8 telephone safety follow-up contacts approximately 2 weeks after each of the first 8 doses.
- 3 visits for clinical assessments.
- 1 visit for CSF biomarkers (optional).
- 2 visits for amyloid PET scan (in a subset of subjects).
- 6 visits for brain MRI.
- 1 follow-up safety visit at Week 94 (only for subjects not entering the LTE).

Subjects who meet the LTE inclusion and exclusion criteria will be eligible to enter the LTE. Subjects who enter the LTE will have approximately 40 additional planned clinic visits, and up to 8 telephone safety follow-up contacts, as follows:

- 26 outpatient dosing visits.

- 8 telephone safety follow-up contacts approximately 2 weeks after each of the first 8 doses.
- 4 visits for clinical assessments.
- 2 visits for CSF biomarkers (optional).
- 2 visit for amyloid PET scan (in a subset of subjects).
- 7 visits for brain MRI.
- 1 follow-up safety visit.

Subjects who have a change in AD medication (other than study treatment) during the placebo-controlled or LTE period should have an unscheduled visit; all clinical assessments for the primary and secondary endpoints should be performed prior to the change in medication.

Subjects who experience ARIA during the placebo-controlled or LTE period should have unscheduled visits as per the guidelines in Section 7.2.1.

7.3.1. Screening

During the Screening Visit, under a separate initial consent process, subjects can complete the neurocognitive scales (CDR, MMSE, and the Repeatable Battery for Assessment of Neuropsychological Status [RBANS]). This initial neurocognitive screening is intended to reduce the burden on subjects and sites by avoiding unnecessary testing if subjects do not meet key inclusion criteria. If the subject meets inclusion criteria for these 3 scales, then the full consent process must be completed prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process, which would allow the administration of all screening assessments.

The neurocognitive assessments that have exclusion cut points (CDR, MMSE and RBANS) must be performed at Screening Visit 1. The ADAS-Cog 13, ADCS-ADL-MCI and NPI-10 will be performed at Screening Visit 2 within 14 days after Visit 1 and must NOT be performed on the same day as the CDR, MMSE and RBANS. All other cognitive assessments as well as CSF collection may be performed at any time during screening after eligibility is confirmed during Screening Visit 1. The MRI at Screening Visit 2 should be done only after the subject eligibility based on clinical and laboratory criteria is confirmed during Screening Visit 1. The PET scan at Screening Visit 3 should be completed only after the MRI inclusion criterion is met.

Subject eligibility for the study will be determined no more than 60 days prior to study entry. Subjects who fail screening will be permitted to be rescreened once at the Sponsor’s discretion. Subjects who fail screening due to PET, MMSE, CDR, hepatitis B or C results, or abnormal MRI findings will not be allowed to re-screen.

7.3.2. Treatment

Eligible subjects will report to the study site to receive study treatment every 4 weeks for 76 weeks (20 doses). All subjects who meet the LTE inclusion and exclusion criteria will be eligible to enter the LTE and will receive study treatment every 4 weeks for an additional 100

weeks (26 doses), with the first dose administered approximately 4 weeks after the final dose in the placebo-controlled period of the study.

7.3.3. Follow-Up

All subjects participating in the placebo-controlled period are to return to the study site approximately 2 weeks after the final dose for clinical assessments.

Subjects participating in the placebo-controlled period and not entering the LTE are to return to the study site for a follow-up visit at Week 94 (18 weeks after the last dose). The final study visit for these subjects will be Week 94.

Subjects who participate in the LTE are to return to the study site to receive their first LTE dose approximately 4 weeks after their last dose in the placebo-controlled period of the study. A follow-up visit will occur at Week 198 (18 weeks after the last LTE dose). The final study visit for subjects participating in the LTE will be Week 198.

7.4. Study Stopping Rules

Biogen may terminate this study at any time, after informing Investigators. Biogen (or designee) will notify Investigators when the study is to be placed on hold, completed, or terminated.

Dosing may be terminated by the Sponsor at the recommendation of the IDMC, based exclusively on safety and tolerability data or following the futility analysis, or at the discretion of the Sponsor; therefore there are no study-specific stopping rules defined in this protocol.

7.5. End of Study

The end of study is last subject, last visit.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at Screening or at the time point specified in the individual eligibility criterion listed:

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.
2. Aged 50 to 85 years old, inclusive, at the time of informed consent.
3. All women of childbearing potential and all men must practice effective contraception during the study and for 24 weeks after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 15.5.
4. Must have at least 6 years of education or work experience to exclude mental deficits other than MCI or mild AD.
5. Must have a positive amyloid PET scan. Previously obtained PET scan (within 12 months of screening) is permissible for subjects not participating in the PET cohort. Previous PET scan images must be submitted to the central imaging vendor to confirm study inclusion criteria are met.
6. Must meet all of the following clinical criteria for MCI due to AD or mild AD according to NIA-AA criteria [Albert 2011; McKhann 2011], and must have:
   - A CDR-Global Score of 0.5.
   - An RBANS score of 85 or lower indicative of objective cognitive impairment.
   - An MMSE score between 24 and 30 (inclusive).
7. Apart from a clinical diagnosis of early AD, the subject must be in good health as determined by the Investigator, based on medical history and screening assessments.
8. Must consent to apolipoprotein E (Apo E) genotyping.
9. Has one informant/care partner who, in the Investigator's judgment, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally be available by phone to provide information to the Investigator and study staff about the subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study, and the use of the same informant/care partner for the duration of the study is encouraged.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening, or at the time point specified in the individual criterion listed:

Medical History

1. Any uncontrolled medical or neurological/neurodegenerative condition (other than AD) that, in the opinion of the Investigator, might be a contributing cause of the subject's cognitive impairment (e.g., substance abuse, vitamin B_{12} deficiency, abnormal thyroid function, stroke or other cerebrovascular condition, lewy body dementia, fronto-temporal dementia, head trauma)..
2. Clinically significant psychiatric illness (e.g., uncontrolled major depression, schizophrenia, bipolar affective disorder) within 6 months prior to Screening
3. Transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year prior to Screening.
4. Brain MRI performed at Screening (per centrally read MRI) that shows evidence of any of the following:
   - Acute or sub-acute hemorrhage.
   - Prior macrohemorrhage (defined as >1 cm in diameter on T2* sequence) unless it can be documented that the finding is not due to an underlying structural or vascular abnormality (i.e., finding does not suggest subject is at risk of recurrent hemorrhage).
   - Greater than 4 microhemorrhages (defined as ≤1 cm in diameter on T2* sequence).
   - Cortical infarct (defined as > 1.5 cm in diameter).
   - >1 lacunar infarct (defined as ≤ 1.5 cm in diameter).
   - Superficial siderosis.
   - History of diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scale [Wahlund 2001].
   - Any finding that, in the opinion of the Investigator, might be a contributing cause of subject's dementia, might pose a risk to the subject, or might prevent a satisfactory MRI assessment for safety monitoring.
5. History of bleeding disorder or predisposing conditions, blood clotting or clinically significant abnormal results on coagulation profile at Screening, as determined by the Investigator.
6. Poorly controlled diabetes mellitus as defined (according to the National Glycohemoglobin Standardization Program) by a glycosylated hemoglobin (HbA_{1c}) value of ≥ 7%.

7. History of unstable angina, myocardial infarction, chronic heart failure (New York Heart Association Class III or IV), or clinically significant conduction abnormalities (e.g., unstable atrial fibrillation) within 1 year prior to Screening.
8. Clinically significant 12-lead ECG abnormalities, as determined by the Investigator.
9. Uncontrolled hypertension defined as: average of 3 systolic blood pressure [SBP]/diastolic blood pressure [DBP] readings > 165/100 mmHg at Screening (blood pressure measurements exceeding these limits may be repeated as warranted by the Investigator, but values must be within the specified limits for the subject to be eligible for the study), or persistent SBP/DBP readings > 180/100 mmHg 3 months prior to randomization (Day 1) that in the opinion of the Investigator are indicative of chronic uncontrolled hypertension.
10. History of malignancy or carcinoma. The following exceptions may be made after discussion with the Sponsor:
    - Subjects with cancers in remission more than 5 years prior to Screening.
    - Subjects with a history of excised or treated basal cell or squamous carcinoma.
    - Subjects with prostate cancer in situ.
11. History of seizure within 10 years prior to Screening.
12. Indication of impaired liver function as shown by an abnormal liver function profile at Screening (e.g., repeated values of aspartate aminotransferase [AST] and alanine aminotransferase [ALT] $\geq 2 \times$ the upper limit of normal).
13. History or evidence of an autoimmune disorder considered clinically significant by the Investigator or requiring chronic use of systemic corticosteroids or other immunosuppressants.
14. Recent history (within 1 year of Screening) of alcohol or substance abuse as determined by the Investigator, a positive urine drug (due to non-prescription drug) or alcohol test at Screening, or use of cannabinoids (prescription or recreational).
15. Clinically significant systemic illness or serious infection (e.g., pneumonia, septicemia) within 30 days prior to or during Screening.
16. History of or positive test result for human immunodeficiency virus (HIV).
17. History of or positive test result at Screening for hepatitis C virus antibody or hepatitis B virus (defined as positive for hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb]). Subjects with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive hepatitis B surface antibody IgG, and positive HBcAb) are eligible to participate in the study (US Centers for Disease Control and Prevention's interpretation of the hepatitis B serology panel).
18. History of severe allergic or anaphylactic reactions, or history of hypersensitivity to any of the inactive ingredients in the drug product (refer to the IB for information on the clinical formulation).

19. Any other medical conditions (e.g., renal disease) that are not stable or controlled, or, which in the opinion of the Investigator, could affect the subject's safety or interfere with the study assessments.

Medications

20. Any medications that, in the opinion of the Investigator, may contribute to cognitive impairment, put the subject at higher risk for AEs, or impair the subject's ability to perform cognitive testing or complete study procedures.
21. Use of allowed chronic medications at doses that have not been stable for at least 4 weeks prior to Screening Visit 1 or use of AD medications (including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine) at doses that have not been stable for at least 8 weeks prior to Screening Visit 1.
22. Use of medications with platelet anti-aggregant or anti-coagulant properties (the use of aspirin at a prophylactic dose [≤ 325 mg daily] is allowed).
23. Use of illicit narcotic medication.
24. Vaccinations within 10 days prior to randomization (Day 1).
25. Participation in any active immunotherapy study targeting Aβ unless documentation of receipt of placebo is available.
26. Participation in any other passive immunotherapy study targeting Aβ within 48 weeks prior to Screening unless documentation of receipt of placebo is available.
27. Participation in any study with purported disease-modifying effect in AD within 26 weeks prior to Screening unless documentation of receipt of placebo is available. Subjects who developed ARIA-E during a previous disease-modifying trial should be excluded.
28. Participation in a previous study with aducanumab (subject is eligible if he/she did not receive active aducanumab).

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29. Contraindications to having a brain MRI (e.g., pacemaker; MRI-incompatible aneurysm clips, artificial heart valves, or other metal foreign body; claustrophobia that cannot be medically managed).
30. Contraindication to having a PET scan (e.g., inability to lie flat or still for the duration of the scan) or intolerance to previous PET scans (i.e., previous hypersensitivity reactions to any PET ligand or imaging agent, failure to participate in and comply with previous PET scans).
31. A negative PET scan result with any amyloid-targeting ligand within 24 weeks prior to Screening.
32. Have had or plan exposure to experimental radiation within 12 months prior to Screening such that radiodosimetry limits would be exceeded by participating in this study.

33. For subjects who consent to lumbar puncture (LP), any contraindications to having a LP (e.g., platelet count <100,000/µL, lumbar spine deformity). Any symptoms caused by or related to the optional LP during screening must be resolved prior to randomization. Subjects may still participate in the overall study even if participation in the optional LP portion is contraindicated.

Others

34. Female subjects who are pregnant or currently breastfeeding.
35. Previous participation in this study. Subjects who fail screening will be permitted to be rescreened once at the Sponsor's discretion, except those who fail due to PET, MMSE, CDR, hepatitis B or C, or abnormal MRI findings.
36. Subject currently living in an organized care facility with extensive intervention and/or support of daily living activities.
37. Blood donation (≥ 1 unit) within 1 month prior to Screening.
38. Inability to comply with study requirements.
39. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

8.3. Inclusion Criteria for Long-Term Extension

To be eligible to participate in the LTE, subjects must meet the following eligibility criteria at Week 78:

1. Subject must have completed the placebo-controlled period of the study including the Week 78 Visit. Subject must have taken at least 14 doses and not have missed more than 4 consecutive doses. Subjects who do not meet these criteria can enter the LTE only with Sponsor's approval.
2. MMSE score > 15 at the Week 78 Visit.
3. The subject (or the subject's legally authorized representative) has the ability to understand the purpose and risks of the study and provide signed and dated informed consent (or assent) and authorization to use confidential health information in accordance with national and local subject privacy regulations.
4. Female subjects of childbearing potential and male subjects must practice effective contraception during the study and for 24 weeks after their last dose of study treatment.
5. Apart from a clinical diagnosis of AD, the subject must be in good health as determined by the Investigator, based on medical history.
6. Must have the ability to comply with procedures for protocol-related tests.
7. Has one informant/care partner who, in the Investigator's judgment, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally be available by phone to provide information to the Investigator and study staff about the

subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study, and the use of the same informant/care partner for the duration of the study is encouraged.

8.4. Exclusion Criteria for Long Term Extension

Subjects will be excluded from entering the LTE if at Week 78 they have:

any medical or psychiatric contraindication or clinically significant abnormality that, in the opinion of the Investigator, will substantially increase the risk associated with the subject's participation in and completion of the study.

9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

9.1. Screening and Enrollment

Subjects (or their legally authorized representative, where applicable) must provide informed consent before any screening tests are performed (see Section 17.3). During Screening, subjects can complete the neurocognitive scales (CDR, MMSE and RBANS) to determine study eligibility under a separate initial consent process. If the subject meets inclusion criteria for these 3 scales the full consent process must be completed prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process which would allow the administration of all screening assessments. When a subject signs the full informed consent form (ICF), that subject is considered to be enrolled in the study.

The following tests should be repeated prior to dosing if they were performed > 60 days prior to Day 1: confirmation of eligibility criteria, abbreviated medical history, physical examination, ECG, hematology, blood chemistry, serum pregnancy test, and all neurocognitive assessments. Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log.

9.2. Randomization and Registration of Subjects

Subjects will be registered at the Screening Visit and randomized only after all baseline assessments have been completed and the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. No subject may begin treatment prior to assignment of a unique identification number (registration) and randomization. Any subject identification numbers or randomization schedule assignments that are assigned will not be reused even if the subject does not receive treatment. Rescreened subjects will be assigned a new number.

Subjects will be randomized to receive aducanumab low dose: aducanumab high dose: placebo in a 1:1:1 ratio. The randomization will be stratified by site and ApoE ε4 status (carrier or non-carrier), so that approximately 60% to 70% ApoE ε4 carriers are enrolled. Enrollment will also be monitored, via the IRT, such that the population of subjects with mild AD represents a small percentage of the total enrolled in the trial. Subjects who withdraw from the study may not be replaced.

Refer to the Study Reference Guide for details on registration and randomization.

9.3. Blinding Procedures

This study consists of a randomized, double-blind, placebo-controlled period, followed by a dose-blinded LTE with all subjects receiving aducanumab.

For the double-blinded placebo-controlled period, all study staff who conduct subject assessments will be blinded to the subject treatment assignments. The rating health care professionals should remain blinded to treatment assignment as well as subject care management and only have access to the information necessary to carry out their responsibilities as detailed in

Section 4.3.1. As a placebo match is not provided for the study, unblinded pharmacy staff are required to manage all aspects of study drug receipt, dispensing and preparation. To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Biogen or its representatives, except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded Quintiles or Biogen safety staff.

For the LTE, the dose information must remain restricted. The rating and treating health care professional should remain blinded to treatment assignment and only have access to the information necessary to carry out their responsibilities as detailed in Section 4.3.1. To maintain the study blind, it is imperative that dose information is not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Biogen or its representatives, except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded Quintiles or Biogen safety staff.

10. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

A subject *must* permanently discontinue study treatment for any of the following reasons:

- The subject develops any of the following:
  - ARIA-E accompanied by severe or serious clinical symptoms.
  - Symptomatic ARIA-H (microhemorrhages or superficial siderosis) with severe or serious clinical symptoms.
  - ARIA-H with ≥ 10 microhemorrhages and/or ≥ 2 focal areas of superficial siderosis.

  See Section 7.2.1 for full details regarding discontinuation and dose reduction due to ARIA-E or ARIA-H.
- The subject becomes pregnant. Study treatment must be discontinued immediately and pregnancy must be reported according to the instructions in Section 15.4.1.
- The subject withdraws consent to continue study treatment.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment or unblinding of the subject's treatment assignment.
- The subject experiences an AE that does not resolve or requires continued treatment that meets exclusionary criteria.
- The subject experiences a severe infusion reaction.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Investigator or Sponsor for noncompliance.

The reason for discontinuation of study treatment must be recorded in the subject's case report form (CRF).

Subjects who discontinue treatment should remain in the study and continue protocol-required tests and assessments until the end of the study or until the subjects withdraw consent.

10.2. Withdrawal of Subjects From Study

Subjects must be withdrawn from the study for any one of the following reasons:

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator or Sponsor.

The reason for the subject's withdrawal from the study must be recorded in the subject's CRF.

Subjects who are withdrawn from the study after receiving ≥1 doses of study treatment should complete the Early Termination (ET) Visit after the reason for withdrawal is identified. Subjects should return to the site as soon as possible to complete assessments as outlined in the Week 94 (Follow-up [FU]/ET) Visit if discontinuing during the double-blind period of the study or as outlined in the Week 198 (FU/ET) Visit if discontinuing from the LTE (see Section 4 for details).

11. STUDY TREATMENT USE

11.1. Regimen

Refer to and follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

Please see Section 4.2 (Schedule of Events) for the study drug infusion schedule during the placebo-controlled and LTE periods of the study.

Aducanumab is to be administered by IV infusion following dilution into saline. See Section 12 for details of aducanumab study treatment.

11.1.1. Aducanumab

The Sponsor will provide aducanumab to study sites.

11.1.2. Placebo

Placebo [redacted] sodium chloride) will be supplied by the study site.

11.2. Modification of Dose and/or Treatment Schedule

Refer to Section 7.2.1 (dose suspension) and Section 7.2.2 (infusion interruption). Doses should be administered at least 21 days apart. If the dosing interval cannot be met, the dose administration should be assessed by the study medical monitor.

11.3. Precautions

Not applicable.

11.4. Compliance

Compliance with treatment dosing is to be monitored and recorded by unblinded site staff.

11.5. Prior and Concomitant Therapy and Procedures

11.5.1. Prior and Concomitant Therapy

Prior AD medication use within the 12 months prior to screening will be captured.

A concomitant therapy is any drug or substance administered between the informed consent and the FU/ET Visit (Week 94 or Week 198).

No premedication (e.g., anti-allergy drugs, antipyretic analgesics) should be used prior to the start of study drug infusion unless discussed with the study medical monitor in advance.

11.5.1.1. Allowed Concomitant Therapy

- Medications for chronic conditions are allowed at a stable dose during the study as long as the subject has been stable on the medication(s) for at least 4 weeks prior to Screening Visit 1.
- Symptomatic therapies for AD, including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine, are allowed provided that subjects are receiving a stable dose for at least 8 weeks prior to Screening Visit 1 and that they stay on a stable dose while in the study.
- Vaccinations with live or attenuated vaccines are allowed during the study. Administration of any vaccination/booster should not be given < 10 days prior to any dosing visit and for 10 days after a dosing visit.

11.5.1.2. Disallowed Concomitant Therapy

- Medications with platelet anti-aggregant or anti-coagulant properties, except the use of aspirin at a dose of ≤ 325 mg per day.
- Non-prescription narcotic medication.
- Immunosuppressive drugs (including systemic corticosteroids). Local corticosteroids and certain systemic corticosteroids may be permitted at the Sponsor's discretion.
- Parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange, and plasmapheresis.
- Any investigational drug.

Subjects should be instructed to continue the medications that they were receiving at enrollment (see allowed concomitant therapy above) and avoid starting any new medications or herbal preparations during the study period, as it may confound the results of the study. However, medically indicated medication or treatment should not be withheld. Subjects should inform the Investigator of any changes in medication. The change should be reviewed by the Investigator and the study medical monitor to determine whether the subject's study treatment should be suspended, with the exception of medications used to treat AEs, which would not result in automatic withdrawal. Biogen may be consulted if required.

Subjects should have an unscheduled visit for a change in AD medication, and all clinical assessments for the primary and secondary objectives should be performed prior to the change in medication.

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, routine colonoscopy, bacterial cultures) performed between the time the subject is enrolled in the study and the FU/ET Visit, unless the subjects is being followed for study-related toxicity.

The use of concomitant therapies or procedures defined above must be recorded on the subject's CRF. AEs related to administration of these therapies or procedures must be documented on the appropriate AE CRF.

11.6. Continuation of Treatment

No further provisions are made for access to the study treatment. If aducanumab is proven to be beneficial, all regulatory requirements regarding poststudy access will be met.

12. STUDY TREATMENT MANAGEMENT

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Study treatment vials are for one-time use only; any study treatment remaining in the vial must not be used for another subject.

12.1. Aducanumab

Research Name: BIIB037

Generic Name: Aducanumab

Trade Name(s): Not applicable

Synonyms: Fully human, IgG_1, anti-Aβ monoclonal antibody

Aducanumab is a recombinant human antibody expressed in a Chinese hamster ovary cell line (41-3D17), purified to a high degree of purity and formulated as a liquid. Aducanumab is an IgG_1 consisting of 2 heavy and 2 kappa light chains connected by inter-chain disulfide bonds. Aducanumab has 1 carbohydrate moiety linked to Asn-304. Aducanumab is purified from the media and formulated as a liquid.

Aducanumab is supplied as a liquid drug product containing aducanumab CCI sodium citrate CCI citric acid CCI L-arginine hydrochloride CCI polysorbate 80 CCI (weight/volume), pH 6.3. Aducanumab is manufactured in accordance with Good Manufacturing Practices.

The contents of the label will be in accordance with all applicable regulatory requirements. Aducanumab should not be used after the expiration date.

12.1.1. Aducanumab Preparation

The individual preparing aducanumab should carefully review the instructions provided in the DHA.

Aducanumab is to be administered by IV infusion following dilution into saline.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the vials or drug it should not be used. The vial in question should be saved at the study site, and the problem immediately reported to Biogen.

12.1.2. Aducanumab Storage

Study treatment must be stored in a secure location. Aducanumab is to be stored at 2° to 8°C (36°F to 46°F), in a locked storage container with limited access. Aducanumab should be protected from light, protected from freezing, and should not be shaken. If administration of the prepared aducanumab is delayed for more than 2 hours, then it should be kept at 2° to 8ºC until use. If administration of the prepared aducanumab is delayed for more than 24 hours, it must be discarded. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

12.1.3. Aducanumab Handling and Disposal

The Investigator must return all used and unused vials of aducanumab as instructed by Biogen (or its designee), unless approved for onsite destruction.

If any aducanumab supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from Biogen by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Biogen must be notified in writing of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. Aducanumab Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), and accounts of any study treatment accidentally or deliberately destroyed.

Unless otherwise notified, all vials both used and unused, must be saved for study treatment accountability. By the end of the study reconciliation must be made between the amount of aducanumab supplied, dispensed, and subsequently destroyed or returned to Biogen. A written explanation must be provided for any discrepancies.

12.2. Placebo

The placebo [redacted]sterile sodium chloride for injection) will be provided by the site in the form of 100 ml saline IV bags.

12.3. Additional Protocol-Designated Products

Refer to the DHA for infusion-related supply specifications.

For details on PET imaging ligands, refer to the procedural manual for PET.

13. EFFICACY, PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS

Refer to Section 4.2 for the timing of assessments.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of aducanumab:

- CDR
- MMSE
- ADAS-Cog 13
- ADCS-ADL-MCI
- NPI-10

It is recommended that clinical assessments be performed at the same time of day for patients during their study visits.

Some tests will require the informant/care partner to participate and answer questions regarding the subject's daily activities and cognitive capabilities.

The order of administration of the clinical assessments is described in the Study Reference Guide.

13.2. Pharmacokinetic Assessments

Serum concentrations of aducanumab will be measured using a validated assay.

13.3. Pharmacodynamic Assessments

The following tests will be performed to assess the pharmacodynamic properties of aducanumab:

- Serial measurement of amyloid plaque burden in certain areas of the brain as measured by amyloid PET (in a subset of approximately 400 subjects participating in the PET cohort).

  Only sites with capabilities of performing ^{18}F-florbetapir PET will be allowed to perform this assessment. Investigator participation in this part of the study is optional and contingent upon approval by his/her ethics committee (EC) or institutional review board (IRB). If the Investigator is not participating or the test is not approved by his/her EC/IRB, the relevant section of the ICF will not be applicable to that site.

  Subject participation in this part of the study is optional at participating sites. Informed consent must be recorded in the CRF. Detailed PET scanning protocols will be described in a separate procedural manual for PET. Approximately 400 subjects are expected to participate in this part of the study.

- Whole brain volume, hippocampal volume, ventricle volume, and cortical gray matter volume measured by MRI.

  Detailed MRI scanning protocols will be described in the procedural manual for MRI.

- Functional connectivity as measured by tf-fMRI (in a subset of sites and subjects).

  Only sites with capabilities of performing tf-fMRI will be allowed to perform this assessment. Detailed tf-fMRI scanning protocols will be described in the procedural manual for MRI.

- Cerebral blood flow as measured by ASL-MRI (in a subset of sites and subjects).

  Only sites with capabilities of performing ASL-MRI will be allowed to perform this assessment. Detailed ASL-MRI scanning protocols will be described in the procedural manual for MRI.

- Disease-related blood and CSF biomarkers. Subject participation in CSF collection is optional (see Section 13.4.1).

13.4. Additional Assessments

13.4.1. CSF Biomarkers (Lumbar Puncture Test)

An optional CSF collection will be conducted at sites. Investigator participation in this part of the study is optional and contingent upon approval by the site's EC/IRB. If the Investigator is not participating or the test is not approved by the site's EC/IRB, the relevant section of the ICF will not be applicable to that site.

Subject participation in the LP test is optional at participating sites. Informed consent must be recorded in the CRF.

Analyses of CSF samples will include, but are not limited to, the following:

- Disease-related biomarker levels (amyloid and tau proteins).
- Cell count and differential (to be conducted by the local laboratory).
- Total protein, (to be conducted by the central laboratory).

Four LPs are to be performed (1 at Screening, 1 in the placebo-controlled period, and 2 in the LTE). Any symptoms caused by or related to the LP must be resolved or stabilized, in the opinion of the Investigator, prior to infusion. Vital signs will be obtained before the LP at each visit for subjects participating. Guidance on LPs will be provided in the Study Reference Guide.

13.4.2. ApoE genotyping

Whole blood samples for deoxyribonucleic acid (DNA) ApoE genotyping will be collected from all subjects at the Screening Visit.

13.4.3. Optional DNA Test

Additional whole blood samples for DNA analysis will be collected only for subjects that consent to this optional test. Samples will be collected and archived according to the guideline in the laboratory manual to support discovery and verification of biomarkers related to AD or aducanumab pharmacology.

13.4.4. Health Outcomes Assessments

The following assessments will be performed to evaluate the effect of aducanumab in subjects and caregivers:

- EQ-5D (SR)
- EQ-5D (IR-S)
- EQ-5D (IR-I)
- mPDQ-20
- Caregiver burden questionnaire

Some tests will require the informant/care partner to participate and answer questions regarding the subject's daily activities and cognitive capabilities.

The order of administration of the clinical assessments is described in the Study Reference Guide.

14. SAFETY ASSESSMENTS

See Section 4.2 for the timing of assessments.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of aducanumab:

- AE and SAE monitoring.
- Physical examination, including height and weight.
- Neurological examination.
- Vital signs (body temperature, heart rate, SBP, DBP, and respiratory rate).
- 12-lead ECG.
- Brain MRI.
- Concomitant medication, therapy and procedure monitoring.
- MOCA (for ARIA monitoring and management).
- Columbia Suicide Severity Rating Scale.

14.2. Laboratory Safety Assessments

The following laboratory assessments will be performed to evaluate the safety profile of aducanumab

- Hematology: complete blood count with differential and platelet count, and absolute neutrophil count.
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, ALT, AST, lactate dehydrogenase, gamma-glutamyl-transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, potassium.
- Urinalysis: color, specific gravity, pH, protein, glucose, blood ketones, and microscopic examination (if abnormal).
- Serum and urine pregnancy test for women of childbearing potential only.
- Coagulation, virology (including HIV if dictated by local law), HbA_{1c}, and alcohol/drug screen at Screening.

14.3. Immunogenicity Assessments

Presence of serum anti-aducanumab will be determined using a validated assay. A standard 3-tier anti-drug antibody (ADA) approach will be used (i.e., screening assay, confirmatory assay,

and titration assay). Confirmed antidrug antibody-positive samples will be tested for the presence of anti-aducanumab neutralizing antibodies using a validated assay.

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject or his/her legally authorized representative must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Determination of whether an abnormal laboratory value meets the definition of an AE will be made by the Investigator. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE.
- A laboratory test result that requires the subject to receive specific corrective therapy.
- A laboratory abnormality that the investigator considers to be clinically significant.

15.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes

listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

15.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject is hospitalized. The study site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
    - If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 15.1.2 is met.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2.
- The relationship of the event to study treatment as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment.

Relationship of Event to Study Treatment	
Not related	An AE will be considered "not related" to the use of the investigational drug if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include but are not limited to: the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of the investigational drug if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of an alternative explanation for the AE.

15.2.3. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by Biogen according to the IB for aducanumab.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and the FU/ET visit is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment.

15.3.2. Adverse Events of Special Interest

ARIA-E and ARIA-H are considered AEs of special interest and will be entered on the Adverse Event of Special Interest CRF within 72 hours following the receipt of abnormal MRI findings from the central MRI reader.

AE reporting for ARIA-E and ARIA-H will be based on the following centrally read MRI sequences: fluid attenuated inversion recovery/T2 for ARIA-E and T2*/gradient echo for ARIA-H.

If the event qualifies as an SAE an SAE form should be submitted per the guidelines in Section 15.3.4. Investigators should include a copy of the centrally read MRI report when submitting the SAE form to Quintiles Lifecycle Safety.

15.3.3. Serious Adverse Events

Any SAE experienced by the subject between the time of the signing of the ICF and the FU/ET visit is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to Biogen (or designee) within 24 hours as described in Section 15.3.4. Follow-up information regarding an SAE also must be reported with 24 hours.

Events occurring after the FU/ET visit should be reported to Biogen only if the investigator considers the SAE related to study treatment.

Any SAE that is ongoing when the subject completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

15.3.4. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify Quintiles Lifecycle Safety within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any SAE that occurs between the time that the subject has signed the ICF and the FU/ET Visit must be reported to Quintiles Lifecycle Safety) within 24 hours of the study site staff becoming aware of the event. Thereafter, the event should be reported only if the Investigator considers it related to study treatment.

A report ***must be submitted*** to Quintiles Lifecycle Safety regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject has received study treatment
- The severity of the event
- The relationship of the event to study treatment

To report initial or follow-up information on an SAE, fax or email a completed SAE form. Refer to the Study Reference Guide for country-specific Quintiles Lifecycle Safety fax numbers or email PPD

15.3.4.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Quintiles Lifecycle Safety. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.5. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen to be related to the study treatment administered.

Appropriate personnel in Biogen Safety and Benefit Risk (SABR) will unblind SUSARs for the purpose of regulatory reporting. Biogen or designee will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Biogen or designee will submit SUSARs to Investigators in a blinded fashion.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

Subjects should not become pregnant or impregnate their partners during the study and for 24 weeks after their last dose of study drug. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy occurring in a female subject by faxing the appropriate form to Quintiles Lifecycle Safety within 24 hours of the study site staff becoming aware of the pregnancy at the SAE reporting fax number provided in the study reference manual. The Investigator or study site staff must report the outcome of the pregnancy to Quintiles Lifecycle Safety.

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period.

15.4.2. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on an Overdose form and faxed to Quintiles Lifecycle Safety within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Quintiles Lifecycle Safety even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed to Quintiles Lifecycle Safety). All study treatment-related dosing information must be recorded on the dosing CRF.

15.4.3. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator (or designee) should contact the Quintiles 24-hour emergency medical support number. Refer to the Study Reference Guide's Official Contact List for complete contact information.

15.4.3.1. Unblinding for Medical Emergency

In this study, emergency decoding will be made available to the Investigator and designated personnel at Biogen through IRT.

In a medical emergency when knowledge of the subject's treatment assignment may possibly influence the subject's clinical care, the Investigator may access the subject's treatment assignment by IRT. However, prior to unblinding, the Investigator can contact the Quintiles 24-hour emergency medical support number at PPD

The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, nor to personnel involved with the analysis and conduct of the study.

15.5. Contraception Requirements

For the purposes of this study, women of childbearing potential are defined as all women physiologically capable of becoming pregnant, UNLESS they meet one of the following conditions:

- Postmenopausal: 12 months of natural (spontaneous) amenorrhea without an alternative medical cause or 6 weeks after surgical bilateral oophorectomy with or without hysterectomy.
- Post hysterectomy.
- Female surgical sterilization (e.g., bilateral tubal ligation).

For the purposes of the study, highly effective contraception is defined as use of 1 of the following:

- For females of childbearing potential:
  - Established use of oral, injected, or implanted hormonal methods of contraception.
  - Placement of an intrauterine device or intrauterine system.
  - Barrier methods of contraception with use of a spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide.

  - Male sexual partners underwent surgical sterilization with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate.

- For males:
  - Vasectomy with negative semen analysis at follow-up.
  - Use of condoms with spermicide.
- For males and females of childbearing potential:
  True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies and follow up on the outcome of the pregnancy in female subjects.
- Complete an SAE form for each SAE and fax it to Biogen SABR (or designee) within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to Biogen SABR (or designee) within 24 hours of the study site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE follow-up information, if possible, until the event has resolved or become stable.
- Report SAEs to local EC/IRBs, as required by local law.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor (Quintiles) is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen (or designee) is to notify all appropriate regulatory authorities, central EC/IRBs, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Demography and Baseline Disease Characteristics

Demographics and baseline data will be summarized by treatment group with summary statistics (mean, standard deviation [SD], median, and range) or with frequency distributions.

16.2. Efficacy and Pharmacodynamics

16.2.1. Analysis Population

The intent-to-treat (ITT) population, defined as all subjects who were randomized and received at least 1 dose of study treatment (aducanumab or placebo), will be used for the efficacy analyses. For each endpoint, additional conditions may apply to the definition of the population for the analysis. Subjects will be analyzed in the groups to which they were randomized.

16.2.2. Methods of Analysis

16.2.2.1. General Considerations

Summary statistics will be presented. For continuous endpoints, summary statistics will generally include: number of subjects with data, mean, standard deviation, median, and range. For categorical endpoints, this will generally include: number of subjects randomized or dosed, number with data, and the percent of those with data in each category. Statistical testing for efficacy endpoints will be made between each aducanumab regimen and placebo. All statistical tests will be 2-sided.

16.2.2.2. Dose Regimens to be Evaluated

The following dose regimens of aducanumab as compared with placebo will be evaluated

- Aducanumab high-dose regimen (6 mg/kg in ApoE ε4 carriers and 10 mg/kg in ApoE ε4 non carriers).
- Aducanumab 6 mg/kg dose regimen (6 mg/kg in ApoE ε4 carriers and ApoE ε4 non-carriers).
- Aducanumab low-dose regimen (3 mg/kg in ApoE ε4 carriers and 6 mg/kg in ApoE ε4 non-carriers).

In the event that the proposed maximum dose (10mg/kg in ApoE ε4 non-carriers or 6 mg/kg in ApoE ε4 carriers) is terminated after the start of the study (Section 5.3.2) the definition of aducanumab high dose regimen and aducanumab low dose regimen will be modified as shown in Table 10. The dosing modification will be entirely based on interim analysis of outcomes that are independent of, and uninformative about, the treatment-related efficacy effect. Control of

Type I error rate is thus maintained without a statistical adjustment for such adaptations[Chow and Chang 2011].

Table 10: Dose Group Pooling Strategy in the Event of Treatment Group Termination

Treatment group(s) Terminated	Definitions of Revised Pooled Treatment Groups for Comparison
ApoE ε4 carrier high-dose group(6 mg/kg)	Low: ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg High: ApoE ε4 carrier 3 mg/kg and non-carrier 10 mg/kg
ApoE ε4 non-carrier high-dose group (10 mg/kg)	Low: ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg High: ApoE ε4 carrier 6 mg/kg and non-carrier 6 mg/kg
ApoE ε4 carrier high-dose group(6 mg/kg) AND ApoE ε4 non-carrier high-dose group(10 mg/kg)	ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg

16.2.2.3. Considerations for Multiple Comparison Adjustments

A sequential (closed) testing procedure will be used to control the overall Type I error rate due to multiple comparisons for the primary endpoint. The order of treatment comparisons is as follows: aducanumab high-dose regimen versus placebo, aducanumab 6 mg/kg regimen versus placebo, and aducanumab low-dose regimen versus placebo. In the event of a dosing modification (see Table 10), the first comparison is the aducanumab high-dose regimen versus placebo and the second comparison is the aducanumab low-dose regimen versus placebo. If the first comparison is statistically significant ($p \leq 0.05$), then the second comparison will also be made at the 0.05 α level. If the second comparison is statistically significant ($p \leq 0.05$), then the third comparison will also be made at the 0.05 α level. However, all comparisons after the initial comparison with $p > 0.05$ will not be considered statistically significant.

Secondary endpoints have been rank prioritized, in the order shown in Section 6. In order to control for a Type I error for the secondary endpoints, a sequential closed testing procedure will be used and will include both the order of the secondary endpoints and treatment comparisons. Specifically, for each of the secondary endpoints, a sequential (closed) testing procedure, as for the primary endpoint, will be used to control the overall Type I error rate due to multiple treatment comparisons. If statistical significance is not achieved for one, two or all three comparisons, all endpoint(s) of a lower rank will not be considered statistically significant for 1, 2 or all 3 comparisons, respectively.
Due to a current lack of scientific consensus in the AD field on which biomarker(s) might be most appropriate, the selection of the biomarkers and methodology for control of Type I error will be pre-specified in the statistical analysis plan (SAP). Otherwise, there will be no multiple comparison adjustments for the tertiary endpoints.

16.2.2.4. Analysis of the Primary Endpoint

The population for the primary endpoint analysis will be subjects in the ITT population with a baseline and at least one post-baseline CDR-SB score. A mixed model repeated measures (MMRM) model will be used as the primary analysis to analyze change from baseline CDR-SB using fixed effects of treatment, time, treatment-by-time interaction, baseline CDR-SB, baseline CDR-SB by time, baseline MMSE, and baseline ApoE ε4 status.

16.2.2.5. Analysis of the Secondary Endpoints

16.2.2.5.1. Change from Baseline to Week 78 in MMSE

The population for the analysis will be subjects in the ITT population with a baseline and at least one post-baseline MMSE value. A MMRM model will be used as the primary analysis to analyze change from baseline MMSE using fixed effects of treatment, time, treatment-by-time interaction, baseline MMSE value, baseline MMSE by time interaction and baseline ApoE ε4 status

16.2.2.5.2. Change from Baseline to Week 78 in ADAS-Cog 13

The population will be subjects in the ITT population with a baseline and at least one post-baseline ADAS-Cog 13 score. A MMRM model will be used as the primary analysis to analyze change from baseline ADAS-Cog 13 using fixed effects of treatment, time, treatment-by-time interaction, baseline ADAS-Cog 13, baseline ADAS-Cog 13 by time interaction; baseline MMSE and baseline ApoE ε4 status.

16.2.2.5.3. Change from Baseline to Week 78 in ADCS-ADL-MCI

The population will be subjects in the ITT population with a baseline and at least one post-baseline ADCS-ADL-MCI score. A MMRM model will be used as the primary analysis to analyze change from baseline ADCS-ADL-MCI using fixed effects of treatment, time, treatment-by-time interaction, baseline ADCS-ADL-MCI, baseline ADCS-ADL-MCI by time interaction; baseline MMSE and baseline ApoE ε4 status.

16.2.2.6. Tertiary Endpoints Analysis

16.2.2.6.1. Placebo-Controlled Period

Where appropriate, a MMRM model will be used as the primary analysis to analyze change from baseline using fixed effects of treatment, time, treatment by time interaction, baseline value, baseline value by time interaction, baseline MMSE and baseline ApoE ε4 status.

Otherwise, an analysis of covariance or its non-parametric equivalent may be used to analyze these exploratory endpoints.

16.2.2.6.2. Long-Term Extension

The additional endpoints for the LTE are change from baseline over the placebo-controlled and LTE periods of the study. Analyses will be presented by treatment group in the

placebo-controlled period using the placebo-controlled period baseline. Details of the analyses will be pre-specified in the SAP.

16.3. Pharmacokinetics

16.3.1. Analysis Population

The population for PK analysis is defined as all subjects who were randomized, were dosed with study treatment, and had at least 1 measurable aducanumab concentration in serum.

16.3.2. Method of Analysis

The population PK characteristics of aducanumab will be determined by nonlinear mixed effects approach. Covariates that might influence the disposition of aducanumab (e.g., body weight, age, sex, immunogenicity, ApoE ε4 status) will be evaluated and the potential exposure-response relationships will be explored.

16.4. Safety

16.4.1. Analysis Population

The safety population is defined as all subjects who received at least 1 dose of study treatment (including placebo and aducanumab).

16.4.2. Methods of Analysis

All AEs, laboratory data, ECG, neurological and physical examinations and vital signs will be evaluated for safety.

16.4.2.1. Adverse Events

Only treatment-emergent adverse events (TEAEs) will be presented in the summary tables. Treatment emergent is defined as having an onset date that is on or after the start of study treatment, or as worsening after the start of study treatment.

Incidence of TEAEs will be summarized by treatment groups, overall, by severity, and by relationship to study treatment for the placebo-controlled period and over the 24-month LTE. The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

16.4.2.2. Clinical Laboratory Results

Laboratory data will be summarized using shift tables. Shifts from baseline to high/low status for hematology and blood chemistry parameters, and shifts from baseline to high/positive status for urinalysis will be presented. In addition, the shift from baseline to the maximum post-baseline value and the shift from baseline to the minimum post-baseline status will be presented for each laboratory test by treatment group. Also, summaries of laboratory values categorized

based on common toxicity criteria grade will be created. Summary statistics for actual values and change from baseline will also be presented for quantitative laboratory data.

16.4.2.3. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities.

16.4.2.4. ECG

The number and percentage of subjects with shifts to categorical values (abnormal not AE, or abnormal AE) will be summarized by treatment group.

16.4.2.5. Columbia Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale data will be summarized by treatment group.

16.5. Immunogenicity Data

16.5.1. Analysis Population

The analysis population for immunogenicity is defined as all subjects in the safety population who have at least 1 post-dose sample evaluated for immunogenicity.

16.5.2. Methods of Analysis

Anti-aducanumab serum antibodies will be summarized using shift tables.

16.6. Interim Analyses

16.6.1. Interim Futility Analysis

An interim analysis for futility of the primary endpoint will occur after approximately 50% of the subjects have completed the Week 78 Visit (or discontinued). In order to maintain the treatment blind, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim futility analysis. This independent group will present the unblinded interim analysis to the IDMC. The IDMC may recommend terminating the study for futility if it is evident that the efficacy of aducanumab is unlikely to be achieved.

The futility criteria will be discussed in detail in the SAP.

16.6.2. Interim Superiority Analysis

An interim analysis for superiority will be performed after approximately 50% of the subjects have completed the Week 78 Visit (or discontinued). The Lan-Demets method with O'Brien-Fleming stopping boundary for efficacy will be used. In order to maintain the treatment blind, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim superiority analysis. The independent group will present the unblinded interim analysis to the IDMC. The aim of this interim analysis is to allow the possibility to demonstrate treatment effect early. The analysis will be discussed in detail in the SAP.

16.7. Sample Size Considerations

The study's sample size is based, in part, on results from a protocol-specified interim analysis from Study 221AD103 which included 1 year data from 1, 3 and 10 mg/kg treatment groups.

A sample size of 450 subjects per treatment group will have approximately 90% power to detect a true mean difference of 0.5 in change from baseline CDR-SB at Week 78 between the 2 treatment groups. This power calculation is based on a 2-sided t-test assuming equal variance with a final significance level of 0.05, a SD of 1.92 and a drop-out rate of 30%. The SD estimate of 1.92 for Week 78 reflects a 39% increase over the SD from the protocol-specified interim analysis of 1-year data.

The assumed true mean difference of 0.5 between the 2 treatment groups represents an approximately 25% reduction in the placebo mean change from baseline at Week 78 if the placebo mean change is estimated to be 2.

The sample size may be reassessed in a blinded manner approximately 3 months before enrollment is complete if at least 15% of the data are available on the primary endpoint. At this interim time-point, the SD for the primary endpoint will be estimated based on the blinded data. The sample size may be increased if the SD is estimated to be more than approximately 2.07. In addition, the sample size could be increased using external clinical trial results that become available after the start of the study.

17. ETHICAL REQUIREMENTS

Biogen, Quintiles, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated

17.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

17.2. Ethics Committee/Institutional Review Board

The Investigator must obtain EC/IRB approval of the protocol, ICF, and other required study documents prior to starting the study. Biogen will submit documents on behalf of the investigational sites worldwide in compliance with local requirements.

If the Investigator makes any changes to the ICF, Biogen must approve the changes before the ICF is submitted to the EC. A copy of the approved ICF must be provided to Biogen. After approval, the ICF must not be altered without the agreement of the relevant EC and Biogen.

It is the responsibility of the Investigator(s) to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

Biogen must receive a letter documenting EC/IRB approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the EC/IRB at required intervals and not less than annually.

At the completion or termination of the study, the investigational site must submit a close-out letter to the EC/IRB and Biogen

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject’s legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations. Subjects can complete the neurocognitive scales (CDR, MMSE and RBANS) as an initial screening under a separate consent process. If the subject meets inclusion criteria for these 3 scales, the full consent process must be completed

prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process that would allow the administration of all screening assessments.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject (or the subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

A copy of the signed and dated ICF must be given to the subject, caregiver and/or legally authorized representative. The signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the subject's medical record.

17.4. Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., Protected Health Information authorization in North America).

The subject will not be identified by name in the CRF or in any study reports and these reports will be used for research purposes only. Biogen, its partner(s) and designee(s), EC/IRBs, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

17.5. Compensation for Injury

Biogen maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in Biogen or its partner[s]) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

Biogen will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by Biogen. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

During and/or after completion of the study, quality assurance officers named by Biogen or the regulatory authorities may wish to perform onsite audits. The Investigator will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested.

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor(s) will visit the Investigator(s) at regular intervals during the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contract(s) between the institution, Investigator, and Biogen.

18.5. Publications

Details are included in the clinical trial agreement for this study.

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

19.1.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of SAE reports. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or randomized, the IRT vendor will provide each study site with appropriate training, access rights and a user manual

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a web-based electronic data capture (EDC) tool developed by Quintiles and configured by the EDC vendor.

19.1.4. Central Laboratories for Laboratory Assessments

Biogen has selected a central laboratory service to perform all standard hematology, blood chemistry, and urinalysis testing for the study. This central laboratory will also receive, track, and ship all urine, blood, CSF samples, and DNA for specialized ApoE ε4 genotyping, PK, biomarker, and ADA testing, including aliquots from these samples retained as backup in case original samples are lost or not evaluable. Blood samples collected for future DNA testing will be processed to purify DNA and stored by the central laboratory.

Laboratories performing specialized testing will be identified in regulatory documentation. These laboratories will use appropriately validated or qualified assays to test study samples.

19.1.5. Central Facility for Other Assessments

A central imaging laboratory has been selected by Biogen to read and interpret all MRIs for this study within the timeframe specified in the procedural manual for MRI. In cases of ARIA-E and ARIA-H, the central imaging laboratory must expedite notification to the Principal Investigator and the Sponsor. For the purposes of study conduct, the MRI interpretations from the central reader will prevail over those from the local radiologist.

The central imaging laboratory will also collect PET scans and assess the screening scan for eligibility criteria.

19.1.6. Neurocognitive Assessments

Biogen selected a rater management group to establish rater qualification, study specific training and oversight. The study raters are required to complete qualifications steps and required training prior to administering study assessments. The rater management group will oversee the assessments per project-specific plans.

19.2. Study Committees

19.2.1. Advisory Committee

An advisory committee will be formed to provide scientific and medical direction for the study and to oversee the administrative progress of the study. The advisory committee will meet at least 4 times a year to monitor subject accrual and to monitor compliance with the protocol at individual study sites. The advisory committee will be blinded to subject treatment assignments during the study.

Members of the advisory committee will include external experts in AD medicine and statistics. Biogen will designate one of the participating Investigators to be the chairperson of the advisory committee.

19.2.2. Independent Data Monitoring Committee

The IDMC will be formed to review ongoing safety and tolerability data. Members of the IDMC will not be allowed to participate as investigators in this study. The IDMC will review safety data on an ongoing basis to ensure safe and proper treatment of subjects. The IDMC, based on the nature, frequency, and/or severity of an AE(s) may recommend protocol modification(s), dose suspension, dose termination or study termination. An IDMC charter will provide full guidance on the function and practices to be followed by the IDMC.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the EC/IRB and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the EC/IRB before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, Biogen may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Sections 17.2 and 17.3).

19.4. Ethics Committee/Institutional Review Board Notification of Study Completion or Termination

Where required, the regulatory authorities and EC/IRBs must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator must notify Biogen of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

Biogen will designate one or more of the participating Study Investigators as a signatory for the study report. This determination will be made by several factors including but not limited to the Investigator's experience and reputation in the studied indication, the Investigator's contribution to the study in terms of design, management, and/or subject enrollment, or by other factors determined to be relevant by Biogen.

20. REFERENCES

Albert MS, DeKosky ST, Dickson D, 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(3):270-9.

Alzheimer's Disease International. World Alzheimer Report 2014: Dementia and risk reduction. London: Alzheimer's Disease International (ADI); 2014.

Chow S, Chang M. Adaptive Design Methods in Clinical Trials, Second Edition. Second Edition ed. Boca Raton, FL: Chapman and Hall/CRC; 2011.

Doody RS, Thomas RG, Farlow M, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med. 2014;370(4):311-21; correspondence N Engl J Med. 2014;370(15):1459-60.

Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol. 2010;9(11):1118-27.

Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 2014;13(6):614-29.

Fagan T. Crenezumab Disappoints in Phase 2, Researchers Remain Hopeful. Conference Coverage Series: Alzheimer's Association International Conference (AAIC) 2014 [Internet]. Alzforum Web site. 2014 Jul 22 [cited 2014 Oct 04]. Available from: http://www.alzforum.org/news/conference-coverage/crenezumab-disappoints-phase-2-researchers-remain-hopeful.

Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002;297(5580):353-6. Epub 2002 Jul 20.

Hock C, Konietzko U, Streffer JR, et al. Antibodies against beta-amyloid slow cognitive decline in Alzheimer's disease. Neuron. 2003;38(4):547-54. Epub 2003/05/27.

Jack CR, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013;12(2):207-216.

Koffie RM, Meyer-Luehmann M, Hashimoto T, et al. Oligomeric amyloid beta associates with postsynaptic densities and correlates with excitatory synapse loss near senile plaques. Proc Natl Acad Sci U S A. 2009;106(10):4012-7.

Kuchibhotla KV, Goldman ST, Lattarulo CR, et al. Abeta plaques lead to aberrant regulation of calcium homeostasis in vivo resulting in structural and functional disruption of neuronal networks. Neuron. 2008;59(2):214-25.

Kumar-Singh S, Pirici D, McGowan E, et al. Dense-core plaques in Tg2576 and PSAPP mouse models of Alzheimer's disease are centered on vessel walls. American Journal of Pathology. 2005;167(2):527-43. Epub 2005/07/29.

Lenderking WR, Steenrod A, Rüdell K, et al. Options for Evaluating Treatment Benefit in MCI and Prodromal Alzheimer's Disease: Content Validity of the Perceived Deficits Questionnaire (PDQ) in Patients with Early Symptoms of Cognitive Decline. Advances in Alzheimer's Disease. 2014;3:1-10. Epub March 2014.

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. Alzheimer's and Dementia. 2011;7(3):263-269.

Meyer-Luehmann M, Spires-Jones TL, Prada C, et al. Rapid appearance and local toxicity of amyloid-beta plaques in a mouse model of Alzheimer's disease. Nature. 2008;451(7179):720-4.

Morris JC, Blennow K, Froelich L, et al. Harmonized diagnostic criteria for Alzheimer's disease: recommendations. J Intern Med. 2014;275(3):204-13.

Ostrowitzki S, Deptula D, Thurfjell L, et al. Mechanism of amyloid removal in patients with Alzheimer disease treated with gantenerumab. Arch Neurol. 2012;69(2):198-207. Epub 2011 Oct 10.

Pfeifer M, Boncristiano S, Bondolfi L, et al. Cerebral hemorrhage after passive anti-Abeta immunotherapy. Science. 2002;298(5597):1379. Epub 2002/11/16.

Racke MM, Boone LI, Hepburn DL, et al. Exacerbation of cerebral amyloid angiopathy-associated microhemorrhage in amyloid precursor protein transgenic mice by immunotherapy is dependent on antibody recognition of deposited forms of amyloid beta. J Neurosci. 2005;25(3):629-36. Epub 2005/01/22.

Rozkalne A, Spires-Jones TL, Stern EA, et al. A single dose of passive immunotherapy has extended benefits on synapses and neurites in an Alzheimer's disease mouse model. Brain Res. 2009;1280:178-85.

Sperling RA, Jack Jr CR, Black SE, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: Recommendations from the Alzheimer's Association Research Roundtable Workgroup. Alzheimers Dement. 2011;7(4):367-385.

Spires-Jones TL, Mielke ML, Rozkalne A, et al. Passive immunotherapy rapidly increases structural plasticity in a mouse model of Alzheimer disease. Neurobiol Dis. 2009;33(2):213-20.

Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke. 2001;32(6):1318-22.

Weller RO, Subash M, Preston SD, et al. Perivascular drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and Alzheimer's disease. Brain Pathol. 2008;18(2):253-66.

Wilcock DM, Colton CA. Immunotherapy, vascular pathology, and microhemorrhages in transgenic mice. CNS Neurol Disord Drug Targets. 2009;8(1):50-64. Epub 2009/03/12.

Winkler DT, Bondolfi L, Herzig MC, et al. Spontaneous hemorrhagic stroke in a mouse model of cerebral amyloid angiopathy. J Neurosci. 2001;21(5):1619-27. Epub 2001/02/27.

21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease", and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

Biogen MA Inc.
225 Binney Street
Cambridge, MA 02142
United States

PROTOCOL NUMBER: 221AD302

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead Berkshire
SL6 4AY
United Kingdom

PHASE OF DEVELOPMENT: 3

PROTOCOL TITLE: A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease

EUDRA CT NO: **2015-000967-15**

DATE: 28 June 2018
Version 6.0
FINAL

Supersedes previous Version 5.0 dated 18 September 2017.

SPONSOR SIGNATURE

Protocol 221AD302 was approved by:

PPD

2 July 2018

Date

Biogen MA Inc.

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103-0027
Japan

For 24-hour emergency medical support contact IQVIA at PPD

Please refer to the Study Reference Manual for complete contact information.

Biogen may transfer any or all of its study-related responsibilities to a contract research organization (CRO) and other third parties; however, Biogen retains overall accountability for these activities.

2. LIST OF ABBREVIATIONS

12F6A	recombinant, human anti-β-amyloid immunoglobulin G_1 monoclonal antibody with an amino acid sequence identical to aducanumab, produced in a different Chinese hamster ovary cell line
Aβ	β-amyloid (peptide derived from membrane bound amyloid precursor protein)
AA	Alzheimer's Association
AD	Alzheimer's disease
ADA	antidrug antibody
ADAS-Cog 13	Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items)
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment version)
AE	adverse event
ALT	alanine aminotransferase
ApoE	apolipoprotein E
ApoE ε4	apolipoprotein E4
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid-related imaging abnormality-edema
ARIA-H	amyloid-related imaging abnormality-hemorrhage or superficial siderosis
ASL-MRI	arterial spin labeling magnetic resonance imaging
AST	aspartate aminotransferase
CAM	Caregiver Assessment Measure
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating sum of boxes
ch12F6A	murine IgG_{2a} chimeric version of 12F6A or aducanumab
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	diastolic blood pressure
DHA	Directions for Handling and Administration
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
EDC	electronic data capture
EOT	End of Treatment
EQ-5D	EuroQol health status measure
EQ-5D (IR-I)	EuroQol health status measure, informant reported on

	informant's own health status
EQ-5D (IR-S)	EuroQol health status measure, informant reported on subject
EQ-5D (SR)	EuroQol health status measure, subject self-reported
FU	follow-up
GCP	Good Clinical Practice
HbA_{1c}	glycosylated hemoglobin
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HCP	health care professional
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
Ig	immunoglobulin
IR	informant rated
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous(ly)
IWG	International Working Group
LTE	long-term extension
LP	lumbar puncture
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-model repeated measures
MMSE	Mini-Mental State Examination
MOCA	Montreal Cognitive Assessment
mPDQ-20	Perceived Deficits Questionnaire-20 modified version
MRI	magnetic resonance imaging
NIA	National Institute on Aging
NIA-AA	National Institute on Aging (NIA) at National Institutes of Health (NIH) and the Alzheimer's Association (AA)
NPI-10	Neuropsychiatric Inventory-10
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic(s)
PET	positron emission tomography
PI	Principal Investigator
PK	pharmacokinetic(s)
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
RNA	ribonucleic acid
SABR	Safety and Benefit-Risk

SAE	serious adverse event
SAP	statistical analysis plan
SB	sum of boxes
SBP	systolic blood pressure
SD	standard deviation
SR	subject rated
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
tf-fMRI	task-free functional MRI

3. SYNOPSIS

Protocol Number:	**221AD302**
Protocol Title:	A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease
Version Number:	6.0
Name of Study Treatment:	Aducanumab (BIIB037)
Study Indication:	Alzheimer's Disease
Study Rationale:	The purpose of this Phase 3 study is to assess the efficacy and safety of aducanumab compared with placebo in subjects with early Alzheimer's Disease (AD), including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD. Aducanumab is a human monoclonal antibody that recognizes aggregated forms of β-amyloid (Aβ), including soluble Aβ oligomers and deposited fibrillar Aβ. Interim analyses of the ongoing multiple dose study (Study 221AD103) have demonstrated target engagement, a pharmacodynamic effect on amyloid reduction, and an effect on the Clinical Dementia Rating (CDR)-sum of boxes (SB) and Mini-Mental State Examination (MMSE) suggestive of a reduction in the progression of clinical impairment for aducanumab-treated subjects. These results, along with the observed safety and tolerability profile, warrant further Phase 3 investigation of aducanumab in a patient population spanning the early stages of the AD continuum.
Phase of Development:	3
Study Objectives and Endpoints (placebo-controlled period of the study):	The primary objective of the study is to evaluate the efficacy of monthly doses of aducanumab in slowing cognitive and functional impairment as measured by changes in the CDR-SB score as compared with placebo in subjects with early AD. The primary endpoint that relates to this objective is the change from baseline in CDR-SB score at Week 78. Secondary objectives and endpoints are as follows: To assess the effect of monthly doses of aducanumab as

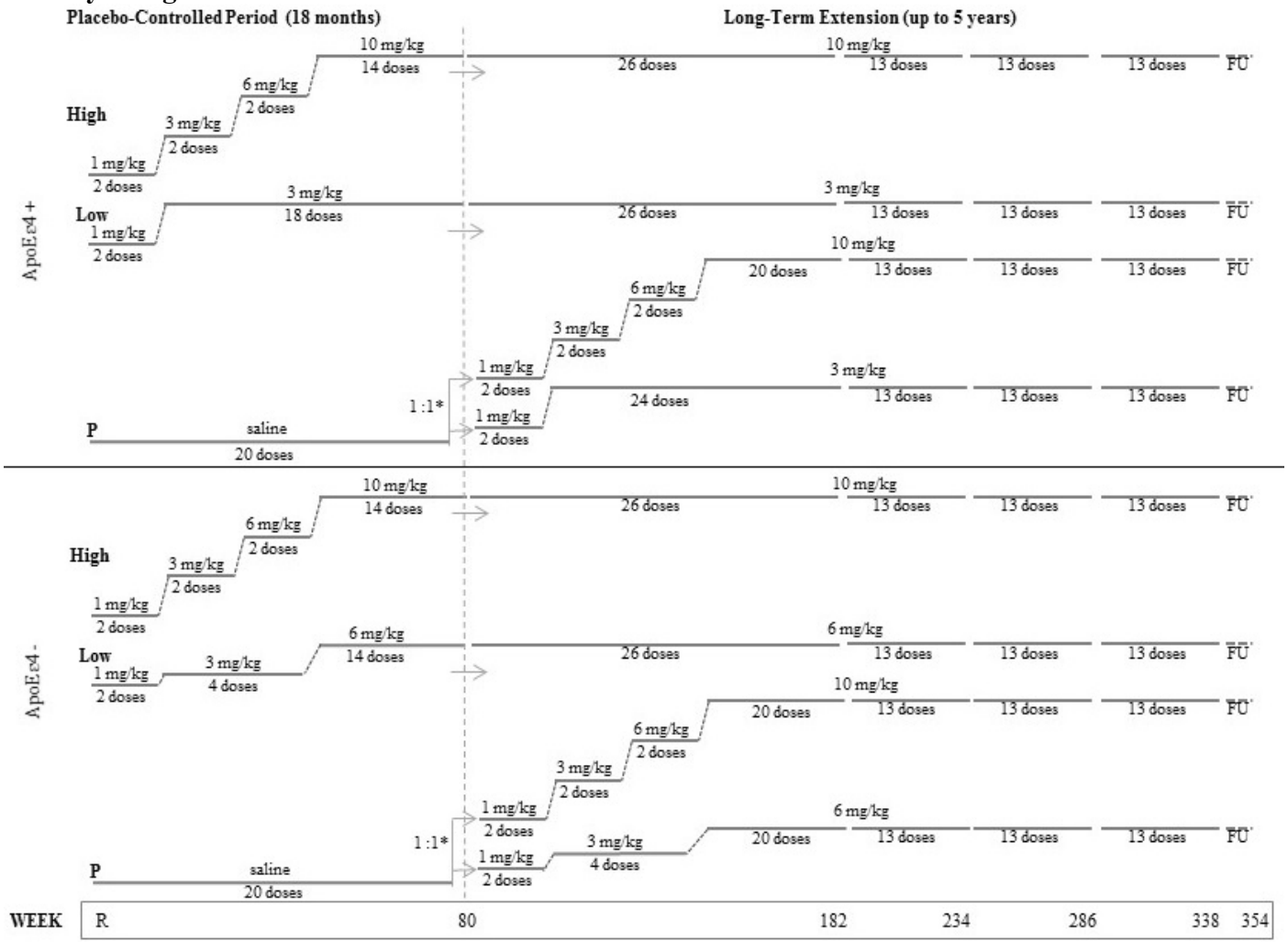
Protocol Number:	**221AD302**
	compared with placebo on clinical progression as measured by • MMSE - Change from baseline in MMSE score at Week 78 • Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13] - Change from baseline in ADAS-Cog 13 at Week 78 • Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI] - Change from baseline in ADCS-ADL-MCI score at Week 78 Tertiary objectives of this study are listed in Section 6.3.1. Tertiary endpoints of this study are listed in Section 6.3.2. Additional exploratory objectives and endpoints are listed in Section 6.4.
Study Objectives and Endpoints (Dose-Blind Long-Term Extension period of the study):	The objectives are to evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD, and to evaluate the long-term efficacy of aducanumab treatment as measured by clinical, radiological, and health-outcomes assessments. Endpoints for the long-term extension (LTE) period of the study are listed in Section 6.5.
Study Design:	Multicenter, randomized study with an 18-month double-blind, placebo-controlled, parallel-group period followed by an optional up to 5-year, dose-blind, LTE period
Study Location:	Approximately 150 sites globally
Number of Planned Subjects:	Approximately 1605 subjects are planned to be enrolled.
Study Population:	This study will be conducted in subjects with early AD, including subjects with MCI due to AD and a subset of mild AD according to National Institute on Aging (NIA) at the National Institutes of Health (NIH) and the Alzheimer's Association (NIA-AA) criteria. Subjects must be positive for amyloid pathology as measured by amyloid positron emission tomography scan. Subjects must be 50 to 85 years old, and apart from the clinical diagnosis of early AD, they must be in good health as determined by the Investigator, based on medical history and the screening assessments. The

Protocol Number:	**221AD302**
	ratio of apolipoprotein E4 (ApoE ε4) carriers to non-carriers in the study population will generally reflect the distribution in the broader AD population. Enrollment will also be monitored, via interactive response technology, such that subjects with mild AD represent a small percentage of the total enrolled in the trial. Detailed criteria are described in Section 8.
Treatment Groups:	For the 18-month placebo-controlled period of the study and based upon their ApoE ε4 carrier status, subjects will be assigned to 1 of 3 treatment groups in a 1:1:1 ratio (aducanumab low dose: aducanumab high dose:placebo) as follows: **ApoE ε4 carrier** **Low dose (3 mg/kg)** **High dose (10 mg/kg)** **Placebo** **ApoE ε4 non-carrier** **Low dose (6 mg/kg)** **High dose (10 mg/kg)** **Placebo** After completion of the placebo-controlled period, subjects may enter a dose-blind LTE study during which all subjects will receive aducanumab for up to 5 years.
Duration of Treatment and Follow Up:	Study duration for each subject participating in the placebo-controlled period only will be approximately 102 weeks (up to an 8-week screening period, 76 weeks of placebo or aducanumab dosing, and 18 weeks of follow-up [FU]). For subjects who enter the optional LTE period, the total study duration will vary and be up to approximately 362 weeks or 83 months (up to an 8-week screening period, 76 weeks of placebo or aducanumab dosing, and 4 weeks of FU, plus an optional LTE period including 256 weeks of dose-blind aducanumab dosing and 18 weeks of FU).

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY 221AD302

4.1. Study Schematic

Figure 1: Study Design



ApoE ε4 +/- = apolipoprotein E4 positive/negative; FU = follow-up; P = placebo; R = randomization date.

*Subjects who are assigned to placebo during the placebo-controlled period are randomized in a 1:1 ratio to high and low dose aducanumab treatment (based upon their ApoE ε4 carrier status) for the long-term extension period on Study Day 1.

4.2. Schedule of Events

Table 1: Placebo-Controlled Period Schedule From Screening Through Week 48

Study Week																		
	Screening (≤ 60 days before Day 1)[1]			**Wk 1, Day 1**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**UV for a Change in AD Medication**
Study Day	**V1**	**V2**	**V3**	**1**	**29 ± 3**	**57 ± 3**	**85 ± 3**	**113 ± 3**	**141 ± 3**	**169 ± 3**	**183 ± 3**	**197 ± 3**	**225 ± 3**	**253 ± 3**	**281 ± 3**	**309 ± 3**	**337 ± 3**	
Initial Screening Consent[2] (optional)	X																	
Full Informed Consent[3]	X																	
Eligibility Criteria	X	X	X	X[4]														
Demography	X																	
Medical History	X	X	X															
Alcohol/Drug Screen	X																	
HbA_{1c}	X																	
HIV[5]/Hepatitis/ Coagulation	X																	
ApoE Genotyping	X																	
DNA (optional)[6]	X																	
Height	X																	
Body Weight	X			X	X	X	X	X	X	X		X	X	X	X	X	X	
Serum Pregnancy Test[7]	X																	
Urine Pregnancy Test[7]				X	X	X	X	X	X	X		X	X	X	X	X	X	
Physical Examination	X						X			X							X	

Study Week																		
	Screening (≤ 60 days before Day 1)[1]			**Wk 1, Day 1**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**UV for a Change in AD Medication**
Study Day	**V1**	**V2**	**V3**	**1**	**29 ± 3**	**57 ± 3**	**85 ± 3**	**113 ± 3**	**141 ± 3**	**169 ± 3**	**183 ± 3**	**197 ± 3**	**225 ± 3**	**253 ± 3**	**281 ± 3**	**309 ± 3**	**337 ± 3**	
Neurological Examination	X						X			X							X	
12-lead Paper ECG	X									X							X	
Vital Signs[8]	X			X	X	X	X	X	X	X		X	X	X	X	X	X	
Hematology, Blood Chemistry and Urinalysis	X			X						X							X	
Randomization				X[9]														
Study Drug Infusion				X	X	X	X	X	X	X		X	X	X	X	X	X	
Anti-Aducanumab Ab[10]				X						X			X					
Aducanumab Concentration[11]				X[12]	X[12]		X[12]	X	X[12]	X[12]		X[12]	X					
RNA, Serum, and Plasma for Biomarkers[13]	X						X	X		X			X					
PBMC Collection	X						X	X		X			X					
CSF Collection (optional)	X[14]																	
Amyloid PET[15]			X								X							
Tau PET[16]			X															
RBANS	X																	
CDR	X										X							X

Study Week																		
	Screening (≤ 60 days before Day 1)[1]			**Wk 1, Day 1**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**UV for a Change in AD Medica-tion**
Study Day	**V1**	**V2**	**V3**	**1**	**29 ± 3**	**57 ± 3**	**85 ± 3**	**113 ± 3**	**141 ± 3**	**169 ± 3**	**183 ± 3**	**197 ± 3**	**225 ± 3**	**253 ± 3**	**281 ± 3**	**309 ± 3**	**337 ± 3**	
MMSE	X										X							X
ADCS-ADL-MCI		X[17]									X							X
ADAS-Cog 13		X[17]									X							X
NPI-10		X[18]									X							
EQ-5D (SR)		X[19]									X							
EQ-5D (IR-S)		X[19]									X							
EQ-5D (IR-I)		X[19]									X							
mPDQ-20		X[19]									X							
CAM		X[19]									X							
C-SSRS				X							X							
AE Reporting				Monitor and record continuously throughout the study														
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study																	
SAE Reporting	Monitor and record continuously throughout the study																	

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version); ApoE = apolipoprotein E; ARIA = amyloid-related imaging abnormalities; CAM = Caregiver Assessment Measure; CDR = Clinical Dementia Rating scale; CRO = contract research organization; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) = EQ-5D, subject self-reported; HbA1c = glycosylated hemoglobin; HIV = human immunodeficiency virus; LTE = long-term extension; MMSE = Mini Mental State Examination; mPDQ-20 = modified Perceived Deficits Questionnaire-20; MRI = magnetic resonance imaging; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; RBANS = Repeatable

Battery for the Assessment of Neuropsychological Status; RNA = ribonucleic acid; SAE = serious adverse event; UV = unscheduled visit; V1, V2, V3 = Screening Visit 1, Screening Visit 2, and Screening Visit 3; Wk = Week.

[1] Examination required for assessment of subject eligibility must be performed at V1. Brain MRI (Table 3) should only be performed once the subject meets eligibility criteria at V1. Amyloid PET should only be performed if the subject meets eligibility criteria at V1 and V2. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.

[2] Subjects may sign this optional form for an initial Screening which allows administration of the RBANS, CDR, and MMSE only, as well as ApoE genotyping.

[3] All subjects must sign this informed consent, including subjects who have signed the optional initial screening consent, once they have met the RBANS, CDR, and MMSE eligibility criteria.

[4] All assessments, including the C-SSRS, must be completed before study treatment administration, except the post-dose sample to measure aducanumab concentration.

[5] HIV testing is at the Investigator's discretion after consideration of risk factors.

[6] Can be collected at any point during and after Screening.

[7] Required for women of childbearing potential only (see Section 15.5).

[8] Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes.

[9] Randomization for both the placebo-controlled period and LTE period will occur on Study Day 1 (see Section 9.2).

[10] Sample collection for anti-aducanumab antibody will be performed prior to study treatment infusion (where applicable).

[11] Blood sampling for aducanumab concentration will be performed prior to infusion

[12] One additional blood sample for aducanumab concentration will be collected between 10 and 60 minutes after completion of the infusion and line flush. Note: For subjects who suspend treatment due to ARIA, only 1 blood sample is required to be collected at each specified visit during the period of dose suspension; all other visits/assessments are required to be performed.

[13] Samples will be collected prior to infusion (where applicable).

[14] May be collected at any point in time during Screening after eligibility at V1 is confirmed but if collected on the same day as an MRI, it should be collected after the MRI is performed. CSF collection at Screening using study-specific procedures is preferred; however, if a CSF sample has been obtained within 3 months prior to Screening, this sample may be used in lieu of requiring that the subject undergo a lumbar puncture at Screening.

[15] Screening amyloid PET is required for all subjects; amyloid PET at Week 26 will only be conducted in selected sites for subjects who are participating in the amyloid PET substudy. The amyloid PET at Week 26 may be scheduled within a window of ±7 days.

[16] Tau PET substudy may be performed in a subset of subjects at selected sites. Baseline tau PET scan must be done during the screening period, after confirmation of amyloid burden by the central imaging CRO (post-Screening V3) but prior to randomization. The screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.

[17] Must be performed within 20 days of V1, but not on the same day as the screening RBANS, CDR, or MMSE.

[18] The NPI-10 can be performed at any time during Screening as long as it is performed after the CDR (e.g., including at Screening V1).

[19] May be performed at any point during Screening after the subject has met eligibility criteria on the RBANS, CDR, and MMSE.

Table 2: Placebo-Controlled Period Schedule From Week 50 to End of Treatment or Follow-Up

Study Week											**FU**[1]
	50	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**78 (EOT)**[2]	**UV for a Change in AD Medication**	**94 (or 18 wks after final dose for subjects who DCT early)**
Study Day	**351 ± 3**	**365 ± 3**	**393 ± 3**	**421 ± 3**	**449 ± 3**	**477 ± 3**	**505 ± 3**	**533 ± 3**	**547 ± 3**		**659 ± 7**
Informed Consent									X[3]		
Eligibility Criteria									X[3]		
Body Weight		X	X	X	X	X	X	X			X
Urine Pregnancy Test[4]		X	X	X	X	X	X	X			X
Physical Examination							X		X		X
Neurological Examination							X		X		X
12-lead Paper ECG							X		X		X
Vital Signs[5]		X	X	X	X	X	X	X			X
Hematology, Blood Chemistry and Urinalysis							X		X		X
Study Treatment Infusion		X	X	X	X	X	X	X			

Study Week											**FU**[1]
	50	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**78 (EOT)**[2]	**UV for a Change in AD Medication**	**94 (or 18 wks after final dose for subjects who DCT early)**
Study Day	**351 ± 3**	**365 ± 3**	**393 ± 3**	**421 ± 3**	**449 ± 3**	**477 ± 3**	**505 ± 3**	**533 ± 3**	**547 ± 3**		**659 ± 7**
Anti-Aducanumab Ab[6]			X						X		X
Aducanumab Concentration[7]		X[8]	X						X		X
RNA, Serum, and Plasma for Biomarkers[9]			X						X		X
PBMC Collection			X						X		X
CSF Collection (optional)									X		
Amyloid PET[10]									X		
Tau PET[11]									X		
CDR	X								X	X	X
MMSE	X								X	X	X
ADCS-ADL MCI	X								X	X	X
ADAS-Cog 13	X								X	X	X
NPI-10	X								X		
EQ-5D (SR)	X								X		

Study Week											**FU**[1]
	50	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**78 (EOT)**[2]	**UV for a Change in AD Medication**	**94 (or 18 wks after final dose for subjects who DCT early)**
Study Day	**351 ± 3**	**365 ± 3**	**393 ± 3**	**421 ± 3**	**449 ± 3**	**477 ± 3**	**505 ± 3**	**533 ± 3**	**547 ± 3**		**659 ± 7**
EQ-5D (IR-S)	X								X		
EQ-5D (IR-I)	X								X		
mPDQ-20	X								X		
CAM	X								X		
C-SSRS		X							X		
AE Reporting	Monitor and record continuously throughout the study										
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study										
SAE Reporting	Monitor and record continuously throughout the study										

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version); ARIA = amyloid-related imaging abnormalities; CAM = Caregiver Assessment Measure; CDR = Clinical Dementia Rating scale; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; DCT = discontinue treatment; ECG = electrocardiogram; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) = EQ-5D, subject self-reported; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MMSE = Mini Mental State Examination; mPDQ-20 = modified Perceived Deficits Questionnaire-20; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; RNA = ribonucleic acid; SAE = serious adverse event; UV = unscheduled visit; wks = weeks.

[1] Subjects who complete the placebo-controlled period and do not enter the LTE are to return to the site for a safety FU Visit at Week 94. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose.

[2] Subjects who discontinue treatment prematurely are to remain in the study, attend a FU Visit 18 weeks after the final dose, and immediately continue protocol-required tests and assessments at a subset of the clinic visits (see Table 10, and Table 11) until the end of the study per the schedule of events. (It is possible that a clinic visit will occur before the FU Visit.) If the FU Visit will occur within 2 weeks of a scheduled clinic visit, then the FU Visit can be combined with the scheduled visit and all assessments required for both visits performed at this single visit. Note: Subjects who withdraw from study prematurely are to return to the site for an EOT Visit; for such subjects, efficacy assessments specified at the EOT visit are not required if the subject

discontinues treatment within 3 months of the previous efficacy assessment visit and no significant changes in cognitive status are suspected by the Investigator. The site should notify the Sponsor in such cases.

[3] Only for subjects entering the long-term extension period.

[4] Required for women of childbearing potential only (see Section 15.5).

[5] Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes.

[6] Sample collection for anti-aducanumab antibody will be performed prior to study treatment infusion (where applicable).

[7] Blood sampling for aducanumab concentration will be performed prior to infusion.

[8] One additional blood sample for aducanumab concentration will be collected between 10 and 60 minutes after completion of the infusion and line flush. Note: For subjects who suspend treatment due to ARIA, only 1 blood sample is required to be collected at each specified visit during the period of dose suspension; all other visits/assessments are required to be performed.

[9] Sample will be collected prior to infusion (where applicable).

[10] Amyloid PET at Week 78 will only be conducted in selected sites for subjects who are participating in the amyloid PET substudy and may be scheduled within a window of ±7 days.

[11] Tau PET substudy may be performed in a subset of subjects at selected sites and may be scheduled within a window of ±7 days. Serial follow-up tau PET scans will be performed after amyloid PET for those subjects also participating in the amyloid PET substudy, but may not be performed on the same day.

Table 3: Brain MRI, ARIA Management, and Follow-Up Phone Call Schedule During the Placebo-Controlled Period

Study Week	**Screening (≤ 60 days before Day 1)**[1]			**Placebo-Controlled Period**													**FU**[2]
				1	**2**	**6**	**10**	**14**	**18**	**22**	**26**	**30**	**42**	**54**	**66**	**78/ EOT**[3]	**Unsched-uled Visit/ MRI for ARIA**[4]	**94 (or 18 wks after final dose for subjects who DCT early)**
Study Day	**V1**	**V2**	**V3**	**1**	**15 ± 3**	**43 ± 3**	**71 ± 3**	**99 ± 3**	**127 ± 3**	**155 ± 3**	**183 ± 3**	**211 ± 3**	**295 ± 3**	**379 ± 3**	**463 ± 3**	**547 ± 3**		**659 ± 7**
Follow-Up Phone Call[5]					X	X	X	X	X	X	X	X						
Brain MRI[6]		X						X		X		X	X	X	X	X	X	X
Aducanumab Concentration[7]										X		X		X			X	X
MOCA				X													X	
RNA, Serum, and Plasma for Biomarkers[8]																	X	
PBMC Collection[8]																	X	

ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality-hemorrhage or superficial siderosis; DCT = discontinue treatment; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; RNA = ribonucleic acid; V1, V2, V3 = Screening Visit 1, Screening Visit 2, and Screening Visit 3; wks = weeks.

1 Brain MRI (V2) will not be performed until the subject has met the eligibility criteria and has acceptable laboratory tests from V1. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.

2 Subjects who complete the placebo-controlled period and do not enter the LTE are to return to the site for a safety FU Visit at Week 94. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose.

3 Subjects who discontinue treatment prematurely are to remain in the study, attend a FU Visit 18 weeks after the final dose, and immediately continue protocol-required tests and assessments at a subset of the clinic visits (see Table 10, and Table 11) until the end of the study per the schedule of events. (It is possible that a clinic visit will occur before the FU Visit.) If the FU Visit will occur within 2 weeks of a scheduled clinic visit, then the FU Visit can be combined with the scheduled visit and all assessments required for both visits performed at this single visit. Subjects who withdraw from study prematurely are

to return to the site for an EOT Visit; for such subjects, efficacy assessments specified at the EOT visit are not required if the subject discontinues treatment within 3 months of the previous efficacy assessment visit and no significant changes in cognitive status are suspected by the Investigator; The site should notify the sponsor in such cases.

[4] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[5] Phone visit may be performed in person if the subject will be at the study site for clinical assessments.

[6] Arterial spin labeling MRI and task-free functional MRI will be performed only at a subset of sites.

[7] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

[8] Sample may be collected ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

Table 4: Long-Term Extension Period Schedule From Week 80 to Week 134

Study Week																	
	80	**84**	**88**	**92**	**96**	**100**	**104**	**106**	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**134**	**UV for a Change in AD Medica-tion**
Study Day	**561 ± 5**	**589 ± 5**	**617 ± 5**	**645 ± 5**	**673 ± 5**	**701 ± 5**	**729 ± 5**	**743 ± 5**	**757 ± 5**	**785 ± 5**	**813 ± 5**	**841 ± 5**	**869 ± 5**	**897 ± 5**	**925 ± 5**	**939 ± 5**	
Body Weight	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Urine Pregnancy Test[1]	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Physical Examination				X			X							X			
Neurological Examination				X			X							X			
12-lead Paper ECG							X							X			
Vital Signs	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Hematology, Blood Chemistry and Urinalysis							X							X			
Anti-Aducanumab Ab[2]	X						X							X			
RNA, Serum, and Plasma for Biomarkers[2]							X							X			
PBMC Collection							X							X			
Aducanumab Concentration[2]	X						X							X			

Study Week																	
	80	**84**	**88**	**92**	**96**	**100**	**104**	**106**	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**134**	**UV for a Change in AD Medica-tion**
Study Day	**561 ± 5**	**589 ± 5**	**617 ± 5**	**645 ± 5**	**673 ± 5**	**701 ± 5**	**729 ± 5**	**743 ± 5**	**757 ± 5**	**785 ± 5**	**813 ± 5**	**841 ± 5**	**869 ± 5**	**897 ± 5**	**925 ± 5**	**939 ± 5**	
Study Treatment Infusion	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
CSF Collection (optional)[3]															X		
Amyloid PET[4]															X		
Tau PET[5]															X		
CDR								X								X	X
MMSE								X								X	X
ADAS-Cog 13								X								X	X
ADCS-ADL-MCI								X								X	X
NPI-10								X								X	
EQ-5D (IR-S)								X								X	
EQ-5D (IR-I)								X								X	
CAM								X								X	
C-SSRS								X								X	
AE Reporting	Monitor and record continuously throughout the study																
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study																
SAE Reporting	Monitor and record continuously throughout the study																

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); CAM = Caregiver Assessment Measure; CDR = Clinical Dementia Rating; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; LTE = long-term extension; MMSE = Mini-Mental State Examination; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; RNA = ribonucleic acid; SAE = serious adverse event; UV = unscheduled visit.

[1] Required for women of childbearing potential only (see Section 15.5).

[2] Sample will be collected prior to infusion (where applicable).

[3] Enrolled subjects who consented to CSF collection during the placebo-controlled period will have the option to consent to CSF collection during the first 2 years of the LTE period.

[4] Only for subjects who participate in the amyloid PET substudy. Amyloid PET may be scheduled within a window of ±7 days.

[5] Tau PET substudy may be conducted at selected sites and may be scheduled within a window of ±7 days. Serial follow-up tau PET scans will be performed after amyloid PET scan for those subjects also participating in the amyloid PET substudy, but may not be performed on the same day.

Table 5: Long-Term Extension Period Schedule From Week 136 to Week 182

Study Week															
	136	**140**	**144**	**148**	**152**	**156**	**160**	**162**	**164**	**168**	**172**	**176**	**180**	**182**	**UV for a Change in AD Medication**
Study Day	**953 ± 5**	**981 ± 5**	**1009 ± 5**	**1037 ± 5**	**1065 ± 5**	**1093 ± 5**	**1121 ± 5**	**1135 ± 5**	**1149 ± 5**	**1177 ± 5**	**1205 ± 5**	**1233 ± 5**	**1261 ± 5**	**1275 ± 5**	
Body Weight	X	X	X	X	X	X	X		X	X	X	X	X	X	
Urine Pregnancy Test[1]	X	X	X	X	X	X	X		X	X	X	X	X	X	
Physical Examination					X							X		X	
Neurological Examination					X							X		X	
12-lead Paper ECG					X							X			
Vital Signs	X	X	X	X	X	X	X		X	X	X	X	X	X	
Hematology, Blood Chemistry and Urinalysis					X							X			
Anti-Aducanumab Ab[2]					X									X	
RNA, Serum, and Plasma for Biomarkers[2]					X									X	
PBMC Collection					X									X	
Aducanumab Concentration[2]					X							X		X	
Study Drug Infusion	X	X	X	X	X	X	X		X	X	X	X	X		
CSF Collection (optional)[3]														X	
Amyloid PET[4]														X	

Study Week															
	136	**140**	**144**	**148**	**152**	**156**	**160**	**162**	**164**	**168**	**172**	**176**	**180**	**182**	**UV for a Change in AD Medication**
Study Day	**953 ± 5**	**981 ± 5**	**1009 ± 5**	**1037 ± 5**	**1065 ± 5**	**1093 ± 5**	**1121 ± 5**	**1135 ± 5**	**1149 ± 5**	**1177 ± 5**	**1205 ± 5**	**1233 ± 5**	**1261 ± 5**	**1275 ± 5**	
Tau PET[5]														X	
CDR								X						X	X
MMSE								X						X	X
ADAS-Cog 13								X						X	X
ADCS-ADL-MCI								X						X	X
NPI-10								X						X	
EQ-5D (IR-S)								X						X	
EQ-5D (IR-I)								X						X	
CAM								X						X	
C-SSRS								X						X	
AE Reporting	Monitor and record continuously throughout the study														
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study														
SAE Reporting	Monitor and record continuously throughout the study														

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); CAM = Caregiver Assessment Measure; CDR = Clinical Dementia Rating; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MMSE = Mini-Mental State Examination; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; RNA = ribonucleic acid; SAE = serious adverse event; UV = unscheduled visit.

[1] Required for women of childbearing potential only (Section 15.5).

[2] Sample will be collected prior to infusion (where applicable).

[3] Enrolled subjects who consented to CSF collection during the placebo-controlled period will have the option to consent to CSF collection during the first 2 years of the LTE period.

[4] Only for subjects who participate in the amyloid PET substudy. Amyloid PET may be scheduled within a window of ±7 days.

[5] Tau PET substudy may be conducted at selected sites and may be scheduled within a window of ±7 days. Serial follow-up tau PET scans will be performed after amyloid PET for those subjects also participating in the amyloid PET substudy, but may not be performed on the same day.

Table 6: Brain MRI, ARIA Management, and Follow-Up Phone Call Schedule From Weeks 80 to 182 of the Long-Term Extension Period

Study Week	**Long-Term Extension**													**Unscheduled Visit for ARIA**[1]
	80	**82**	**86**	**90**	**94**	**98**	**102**	**106**	**110**	**122**	**134**	**158**	**182**	
Study Day	**561 ± 5**	**575 ± 5**	**603 ± 5**	**631 ± 5**	**659 ± 5**	**687 ± 5**	**715 ± 5**	**743 ± 5**	**771 ± 5**	**855 ± 5**	**939 ± 5**	**1107 ± 5**	**1275 ± 5**	
Follow-Up Phone Call[2]		X	X	X	X	X	X	X	X					
Brain MRI[3]					X		X		X	X	X	X	X	X[3]
Aducanumab Concentration[4]														X
MOCA	X													X
RNA, Serum, and Plasma for Biomarkers[5]														X
PBMC Collection[5]														X

ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality-hemorrhage or superficial siderosis; EOT = End of Treatment; LTE = long-term extension; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; RNA = ribonucleic acid.

[1] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[2] Phone visit may be performed in person if the subject will be at the study site for clinical assessments.

[3] Arterial-spin labeling MRI and task-free functional MRI will be performed only at a subset of sites, and will not be performed at any visit after Week 182.

[4] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

[5] Sample may be collected within ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

Table 7: Long-Term Extension Period Schedule From Week 184 to Week 234

Study Week														
	184	**188**	**192**	**196**	**200**	**204**	**208**	**212**	**216**	**220**	**224**	**228**	**232**	**UV for ARIA**[1]
Study Day	**1289 ± 5**	**1317 ± 5**	**1345 ± 5**	**1373 ± 5**	**1401 ± 5**	**1429 ± 5**	**1457 ± 5**	**1485 ± 5**	**1513 ± 5**	**1541 ± 5**	**1569 ± 5**	**1597 ± 5**	**1625 ± 5**	
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine Pregnancy Test[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination							X						X	
Neurological Examination							X						X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology, Blood Chemistry and Urinalysis													X	
RNA, Serum, and Plasma for Biomarkers														X[3]
PBMC Collection														X[3]
Aducanumab Concentration														X[4]
Study Treatment Infusion	X	X	X	X	X	X	X	X	X	X	X	X	X	
Brain MRI													X	X
CDR													X	
MMSE													X	
ADAS-Cog 13													X	
ADCS-ADL-MCI													X	
EQ-5D-(IR-S)													X	
EQ-5D-(IR-I)													X	

Study Week														
	184	**188**	**192**	**196**	**200**	**204**	**208**	**212**	**216**	**220**	**224**	**228**	**232**	**UV for ARIA**[1]
Study Day	**1289 ± 5**	**1317 ± 5**	**1345 ± 5**	**1373 ± 5**	**1401 ± 5**	**1429 ± 5**	**1457 ± 5**	**1485 ± 5**	**1513 ± 5**	**1541 ± 5**	**1569 ± 5**	**1597 ± 5**	**1625 ± 5**	
MOCA														X
C-SSRS													X	
AE Reporting	Monitor and record continuously throughout the study													
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study													
SAE Reporting	Monitor and record continuously throughout the study													

AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version); ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality hemorrhage or superficial siderosis; CDR = Clinical Dementia Rating scale; C-SSRS = Columbia Suicide Severity Rating Scale; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; LTE = long-term extension; MMSE = Mini Mental State Examination; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; RNA = ribonucleic acid; SAE = serious adverse event; UV = unscheduled visit.

[1] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[2] Required for women of childbearing potential only (Section 15.5).

[3] Sample may be collected within ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

[4] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

Table 8: Long-Term Extension Period Schedule From Week 236 to Week 286

Study Week														
	236	**240**	**244**	**248**	**252**	**256**	**260**	**264**	**268**	**272**	**276**	**280**	**284**	**UV for ARIA**[1]
Study Day	**1653 ± 5**	**1681 ± 5**	**1709 ± 5**	**1737 ± 5**	**1765 ± 5**	**1793 ± 5**	**1821 ± 5**	**1849 ± 5**	**1877 ± 5**	**1905 ± 5**	**1933 ± 5**	**1961 ± 5**	**1989 ± 5**	
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine Pregnancy Test[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination							X						X	
Neurological Examination							X						X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology, Blood Chemistry and Urinalysis													X	
RNA, Serum, and Plasma for Biomarkers														X[3]
PBMC Collection														X[3]
Aducanumab Concentration														X[4]
Study Treatment Infusion	X	X	X	X	X	X	X	X	X	X	X	X	X	
Brain MRI													X	X
Amyloid PET[5]							X							
CDR													X	
MMSE													X	
ADAS-Cog 13													X	
ADCS-ADL-MCI													X	
EQ-5D-(IR-S)													X	

Study Week														
	236	**240**	**244**	**248**	**252**	**256**	**260**	**264**	**268**	**272**	**276**	**280**	**284**	**UV for ARIA**[1]
Study Day	**1653 ± 5**	**1681 ± 5**	**1709 ± 5**	**1737 ± 5**	**1765 ± 5**	**1793 ± 5**	**1821 ± 5**	**1849 ± 5**	**1877 ± 5**	**1905 ± 5**	**1933 ± 5**	**1961 ± 5**	**1989 ± 5**	
EQ-5D-(IR-I)													X	
MOCA														X
C-SSRS													X	
AE Reporting	Monitor and record continuously throughout the study													
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study													
SAE Reporting	Monitor and record continuously throughout the study													

AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version); ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality hemorrhage or superficial siderosis; CDR = Clinical Dementia Rating scale; C-SSRS = Columbia Suicide Severity Rating Scale; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; LTE = long-term extension; MMSE = Mini Mental State Examination; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; PK = pharmacokinetic; RNA = ribonucleic acid; SAE = serious adverse event; UV = unscheduled visit.

[1] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[2] Required for women of childbearing potential only (Section 15.5).

[3] Sample may be collected within ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

[4] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

[5] Only for subjects who participate in the amyloid PET substudy. Amyloid PET may be scheduled within a window of ±7 days.

Table 9: Long-Term Extension Period Schedule From Week 288 to the End of Treatment or Follow-Up

Study Week																**FU**[1]
	288	**292**	**296**	**300**	**304**	**308**	**312**	**316**	**320**	**324**	**328**	**332**	**336**	**338 EOT**[2]	**UV for ARIA**[3]	**354 (or 18 wks after final dose for subjects who DCT early)**
Study Day	**2017 ± 5**	**2045 ± 5**	**2073 ± 5**	**2101 ± 5**	**2129 ± 5**	**2157 ± 5**	**2185 ± 5**	**2213 ± 5**	**2241 ± 5**	**2269 ± 5**	**2297 ± 5**	**2325 ± 5**	**2353 ± 5**	**2367 ± 5**		**2479 ± 7**
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Urine Pregnancy Test[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Physical Examination							X							X		X
Neurological Examination							X							X		X
12-lead Paper ECG																X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Hematology, Blood Chemistry and Urinalysis													X			X
Anti-Aducanumab Ab														X		X
RNA, Serum, and Plasma for Biomarkers														X[5]	X[6]	X
PBMC Collection														X[5]	X[6]	X
Aducanumab Concentration														X	X[7]	X
Study Treatment Infusion	X	X	X	X	X	X	X	X	X	X	X	X	X			

Study Week																**FU**[1]
	288	**292**	**296**	**300**	**304**	**308**	**312**	**316**	**320**	**324**	**328**	**332**	**336**	**338 EOT**[2]	**UV for ARIA**[3]	**354 (or 18 wks after final dose for subjects who DCT early)**
Study Day	**2017 ± 5**	**2045 ± 5**	**2073 ± 5**	**2101 ± 5**	**2129 ± 5**	**2157 ± 5**	**2185 ± 5**	**2213 ± 5**	**2241 ± 5**	**2269 ± 5**	**2297 ± 5**	**2325 ± 5**	**2353 ± 5**	**2367 ± 5**		**2479 ± 7**
CSF Collection (optional, if collected at baseline)[8]														X[5]		
Brain MRI														X[9]	X	X[9]
Amyloid PET[10]														X		
Tau PET														X[11]		
CDR														X		X
MMSE														X		X
ADAS-Cog 13														X		X
ADCS-ADL-MCI														X		X
NPI-10														X[5]		
EQ-5D-(IR-S)														X		
EQ-5D-(IR-I)														X		
CAM														X[5]		
MOCA															X	
C-SSRS														X		
AE Reporting	Monitor and record continuously throughout the study															
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study															

Study Week																**FU**[1]
	288	**292**	**296**	**300**	**304**	**308**	**312**	**316**	**320**	**324**	**328**	**332**	**336**	**338 EOT**[2]	**UV for ARIA**[3]	**354 (or 18 wks after final dose for subjects who DCT early)**
Study Day	**2017 ± 5**	**2045 ± 5**	**2073 ± 5**	**2101 ± 5**	**2129 ± 5**	**2157 ± 5**	**2185 ± 5**	**2213 ± 5**	**2241 ± 5**	**2269 ± 5**	**2297 ± 5**	**2325 ± 5**	**2353 ± 5**	**2367 ± 5**		**2479 ± 7**
SAE Reporting	Monitor and record continuously throughout the study															

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version); ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality hemorrhage or superficial siderosis; CAM = Caregiver Assessment Measure; CDR = Clinical Dementia Rating scale; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; DCT = discontinue treatment; ECG = electrocardiogram; EOT = end of treatment; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; FU = follow-up ; LTE = long-term extension; MMSE = Mini Mental State Examination; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; PK = pharmacokinetic; RNA = ribonucleic acid; SAE = serious adverse event; UV = unscheduled visit; wks = weeks.

[1] Subjects who complete the LTE period are to return to the site for a safety FU Visit at Week 354. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose.

[2] Subjects who discontinue treatment prematurely are to remain in the study, attend a FU Visit 18 weeks after the final dose, and immediately continue protocol-required tests and assessments continue protocol-required tests and assessments at a subset of the clinic visits (see Table 11) until the end of the study per the schedule of events. (It is possible that a clinic visit will occur before the FU Visit.) If the FU Visit will occur within 2 weeks of a scheduled clinic visit, then the FU Visit can be combined with the scheduled visit and all assessments required for both visits performed at this single visit. Subjects who withdraw from study prematurely are to return to the site for an EOT Visit. For subjects who discontinue treatment early, efficacy assessments specified at the EOT visit are not required if the subject discontinues treatment within 3 months of the previous efficacy assessment visit and no significant changes in cognitive status are suspected by the Investigator. The site should notify the Sponsor in such cases.

[3] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[4] Required for women of childbearing potential only (see Section 15.5).

[5] This assessment is only to be performed if the EOT Visit is at or before Week 182.

[6] Sample may be collected within ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

[7] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.
[8] Enrolled subjects who consented to CSF collection during the placebo-controlled period will have the option to consent to CSF collection at the EOT Visit.
[9] Arterial-spin labeling MRI and task-free functional MRI will be performed only at a subset of sites, and will not be performed at any visit after Week 182.
[10] Only for subjects who participate in the amyloid PET substudy. Amyloid PET may be scheduled within a window of ±7 days.
[11] This assessment is only to be performed if the EOT Visit is at or before Week 182. Tau PET substudy may be conducted at selected sites and may be scheduled within a window of ±7 days. Serial follow-up tau PET scans will be performed after amyloid PET for those subjects also participating in the amyloid PET substudy, but may not be performed on the same day.

Table 10: Subjects Who Discontinue Study Treatment but Remain in the Study – Placebo-Controlled Period

Study Week	**Placebo-Controlled Period**[1]							
	12	**24**	**26**	**48**	**50**	**72**	**78 (EOT)**[2]	**UV for ARIA**[3]
Study Day	**85 ± 3**	**169 ± 3**	**183 ± 3**	**337 ± 3**	**351 ± 3**	**505± 3**	**547 ± 3**	
Informed Consent							X[4]	
Body Weight	X	X		X		X		
Eligibility Criteria							X[4]	
Physical Examination	X	X		X		X	X	
Neurological Examination	X	X		X		X	X	
12-lead Paper ECG		X		X		X	X	
Vital Signs	X	X		X		X		
Hematology, Blood Chemistry and Urinalysis		X		X		X	X	
RNA, Serum, and Plasma for Biomarkers	X	X					X	X[5]
PBMC Collection								X[5]
Aducanumab Concentration								X[6]
CSF Collection (optional)							X	
Brain MRI[7]							X	X
Amyloid PET[8]			X				X	
Tau PET[9]							X	
CDR			X		X		X	
MMSE			X		X		X	
ADAS-Cog 13			X		X		X	
ADCS-ADL-MCI			X		X		X	

Study Week	**Placebo-Controlled Period**[1]							
	12	**24**	**26**	**48**	**50**	**72**	**78 (EOT)**[2]	**UV for ARIA**[3]
Study Day	**85 ± 3**	**169 ± 3**	**183 ± 3**	**337 ± 3**	**351 ± 3**	**505± 3**	**547 ± 3**	
NPI-10			X		X		X	
EQ-5D (SR)			X		X		X	
EQ-5D (IR-S)			X		X		X	
EQ-5D (IR-I)			X		X		X	
mPDQ-20			X		X		X	
CAM			X		X		X	
MOCA								X
C-SSRS			X				X	
AE Reporting	Monitor and record continuously throughout the study							
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study							
SAE Reporting	Monitor and record continuously throughout the study							

AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version); ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality hemorrhage or superficial siderosis; CAM = Caregiver Assessment Measure; CDR = Clinical Dementia Rating scale; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOT = end of treatment; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) = EQ-5D, subject self-reported; FU = follow-up; LTE = long-term extension; MMSE = Mini Mental State Examination; mPDQ-20 = modified Perceived Deficits Questionnaire-20; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; PK = pharmacokinetic; RNA = ribonucleic acid; SAE = serious adverse event; SoE = schedule of events; UV = unscheduled visit.

[1] Subjects who discontinue study treatment prematurely during the placebo-controlled period are to remain in the study, attend a FU Visit 18 weeks after their final dose as listed in Table 2 and Table 3, and immediately continue protocol-required tests and assessments at a subset of the clinic visits (see Table 10, and Table 11) until the end of the study per the schedule of events. (It is possible that a clinic visit will occur before the FU Visit.) If the FU Visit will occur within 2 weeks of a scheduled clinic visit, then the FU Visit can be combined with the scheduled visit and all assessments required for both visits performed at this single visit. If the subject who discontinued treatment but remained in the study chooses to enroll in the LTE period, he or she will follow the SoE in Table 11.

[2] Subjects who withdraw from study prematurely are to return to the site for an EOT Visit; for such subjects, efficacy assessments specified at the EOT Visit are not required if the subject discontinues treatment within 3 months of the previous efficacy assessment visit and no significant changes in cognitive status are suspected by the Investigator. The site should notify the Sponsor in such cases.

[3] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[4] Only for subjects entering the long-term extension period.

[5] Sample may be collected within ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

[6] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

[7] Arterial spin labeling MRI and task-free functional MRI will be performed only at a subset of sites.

[8] Only for subjects who participate in the amyloid PET substudy. Amyloid PET may be scheduled within a window of ±7 days.

[9] Tau PET substudy may be conducted at selected sites and may be scheduled within a window of ±7 days. Serial follow-up tau PET scans will be performed after amyloid PET for those subjects also participating in the amyloid PET substudy, but may not be performed on the same day.

Table 11: Subjects Who Discontinue Study Treatment but Remain in the Study – Long-Term Extension Period

Study Week	**LTE Period**[1]															
	92	**104**	**106**	**128**	**134**	**152**	**162**	**176**	**182**	**208**	**232**	**260**	**284**	**312**	**338 (EOT)**[2]	**UV for ARIA**[3]
Study Day	**645 ± 5**	**729 ± 5**	**743 ± 5**	**897 ± 5**	**939 ± 5**	**1065 ± 5**	**1135 ± 5**	**1233 ± 5**	**1275 ± 5**	**1457 ± 5**	**1625 ± 5**	**1821 ± 5**	**1989 ± 5**	**2185 ± 5**	**2367 ± 5**	
Body Weight	X	X		X		X		X	X	X	X	X	X	X	X	
Physical Examination	X	X		X		X		X	X	X	X	X	X	X	X	
Neurological Examination	X	X		X		X		X	X	X	X	X	X	X	X	
12-lead Paper ECG		X		X		X		X								
Vital Signs	X	X		X		X		X	X	X	X	X	X	X	X	
Hematology, Blood Chemistry and Urinalysis		X		X		X		X			X		X			
RNA, Serum, and Plasma for Biomarkers		X		X		X			X						X[4]	X[5]
PBMC Collection																X[5]
Aducanumab Concentration																X[6]
CSF Collection (optional)									X						X[4]	
Brain MRI[7]					X				X		X		X		X[7]	X
Amyloid PET[8]									X			X			X	
Tau PET									X						X[9]	
CDR			X		X		X		X		X		X		X	
MMSE			X		X		X		X		X		X		X	
ADAS-Cog 13			X		X		X		X		X		X		X	
ADCS-ADL-MCI			X		X		X		X		X		X		X	
NPI-10			X		X		X		X						X[4]	

Study Week	**LTE Period**[1]															
	92	**104**	**106**	**128**	**134**	**152**	**162**	**176**	**182**	**208**	**232**	**260**	**284**	**312**	**338 (EOT)**[2]	**UV for ARIA**[3]
Study Day	**645 ± 5**	**729 ± 5**	**743 ± 5**	**897 ± 5**	**939 ± 5**	**1065 ± 5**	**1135 ± 5**	**1233 ± 5**	**1275 ± 5**	**1457 ± 5**	**1625 ± 5**	**1821 ± 5**	**1989 ± 5**	**2185 ± 5**	**2367 ± 5**	
EQ-5D-(IR-S)			X		X		X		X		X		X		X	
EQ-5D-(IR-I)			X		X		X		X		X		X		X	
CAM			X		X		X		X						X[4]	
MOCA																X
C-SSRS			X		X		X		X		X		X		X	
AE Reporting	Monitor and record continuously throughout the study															
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study															
SAE Reporting	Monitor and record continuously throughout the study															

AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version);ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality hemorrhage or superficial siderosis; CAM = Caregiver Assessment Measure; CDR = Clinical Dementia Rating scale; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOT = end of treatment; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; FU = follow-up; LTE = long-term extension; MMSE = Mini Mental State Examination; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; NPI 10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; PK = pharmacokinetic; RNA = ribonucleic acid; SAE = serious adverse event; UV = unscheduled visit.

[1] Subjects who discontinue study treatment during the LTE period are to remain in the study, attend a FU Visit as listed in Table 9, and then will continue protocol-required tests and assessments at a subset of the clinic visits.

[2] Subjects who withdraw from study prematurely are to return to the site for an EOT Visit; for such subjects, efficacy assessments specified at the EOT Visit are not required if the subject discontinues treatment within 3 months of the previous efficacy assessment visit and no significant changes in cognitive status are suspected by the Investigator. The site should notify the Sponsor in such cases.

[3] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[4] This assessment is only to be performed if the EOT Visit is at or before Week 182.

[5] Sample may be collected within ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

[6] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.
[7] Arterial-spin labeling MRI and task-free functional MRI will be performed only at a subset of sites, and will not be performed at any visit after Week 182.
[8] Only for subjects who participate in the amyloid PET substudy. Amyloid PET may be scheduled within a window of ±7 days.
[9] This assessment is only to be performed if the EOT Visit is at or before Week 182. Tau PET substudy may be conducted at selected sites and may be scheduled within a window of ±7 days. Serial follow-up tau PET scans will be performed after amyloid PET for those subjects also participating in the amyloid PET substudy, but may not be performed on the same day.

4.3. Additional Information

4.3.1. Site Personnel

A minimum of 3 separate heath care professionals (HCPs) are required:

1. A treating HCP (the Principal Investigator [PI] or Sub-investigator may serve as a treating HCP) who is responsible for the following:
   - Administration of Montreal Cognitive Assessment (MOCA) at Day 1, Week 80, and during management of amyloid-related imaging abnormalities (ARIA) cases.
   - Management of routine neurological care of the subject.
   - Assessment (including assignment of causality) and treatment of adverse events (AEs).
   - Review of selected hematology and blood chemistry results from the central laboratory to assess if the subject's study treatment should be temporarily withheld or permanently discontinued according to the criteria detailed in Section 10.1.
2. An independent rating HCP (designated by the PI of the site) who is responsible for administering the Clinical Dementia Rating (CDR)
3. A second independent rating HCP (designated by the PI of the site) who will administer the Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13], Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI], and the Mini-Mental State Examination (MMSE)

The 2 independent rating HCPs must not be involved with any other aspect of subject care and management and must remain blinded to AEs, concomitant therapy, laboratory data, imaging data, or any other data that have the potential of revealing the treatment assignment. The 2 independent rating HCPs must not share any information about subjects. PIs cannot serve as rating HCPs. The treating HCPs must not discuss AEs (e.g., ARIA) with the independent rating HCPs.

To ensure consistency across sites, rating HCPs must complete the standardized study-specific qualification process on clinical efficacy assessment scoring prior to administration of the specific assessment at their site. All sites must attempt to maintain the same rating HCP throughout the study for specific assessments in an attempt to remain consistent. Each subject should have the same rating HCP perform the subject's specific rating assessment throughout the study. A qualified approved back-up rater should only conduct assessments in place of the primary rater due to extenuating circumstances resulting in unavailability (e.g., due to illness, vacation, or travel). If a rating HCP has to be replaced, the new rating HCP must undergo the study-specific qualification process prior to administration of the assessment.

Hematology and blood chemistry data will be sent to the investigational sites to aid in management of the subject. As with other laboratory and clinical information, these data should NOT be reviewed by the rating HCPs.

The roles of independent raters and treating HCP are NOT interchangeable at the subject level. In addition, the 2 independent raters are not interchangeable at the subject level. If a rater has administered the CDR to a subject, they may not administer the other neurocognitive assessments to that subject at any point during the study.

An unblinded pharmacist (or authorized designee) will be responsible for the storage, distribution, preparation, and accountability of study treatment. The unblinded pharmacist will also be responsible for maintaining the unblinded pharmacy record separate from the main study file in order to support the study blind.

5. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 50% to 75% of all cases. Alzheimer's Disease International estimates that as of 2013, there were 44.4 million people living with dementia worldwide and that this figure will increase to 135.5 million by 2050 [Alzheimer's Disease International 2014].

Clinically, AD is a progressive neurodegenerative disorder characterized by an insidious and unrelenting decline in cognition and behavioral disturbances that result in the person's inability to perform usual activities of daily living [Jack 2013].

Pathologically, AD is defined by the presence in the brain of extracellular neuritic plaques containing β-amyloid (Aβ) peptide and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau proteins. The pathogenesis of these plaques and tangles and how they contribute to the clinical syndrome remain to be fully elucidated, but the leading hypothesis — the "amyloid cascade"— proposes that the driving force behind the disease process is the accumulation of Aβ resulting from an imbalance between Aβ production and Aβ clearance in the brain [Hardy and Selkoe 2002].

The current view of AD, the disease process and its clinical manifestations, is that it manifests along a continuum rather than having categorical stages. Evidence suggests the pathophysiological changes begin years before clinical onset and as the disease progresses, cognitive impairments, behavioral changes, and functional disability manifest [Jack 2013]. Revised criteria for the clinical diagnosis of AD were published by the National Institute on Aging (NIA) at the National Institutes of Health (NIH) and the Alzheimer's Association (AA) [Albert 2011; McKhann 2011; Sperling 2011] and the International Working Group (IWG) [Dubois 2010; Dubois 2014], and a group that included members from both NIA-AA and IWG published recommendations to harmonize the criteria [Morris 2014]. These criteria base the diagnosis of AD on both clinical and biological elements, recognizing the existence of a nonclinical stage of the disease by accepting AD diagnoses prior to signs of dementia using AD biomarkers.

The scientific community has shifted its focus to target patients in the earlier course of the disease continuum with the belief that those patients are more likely to benefit from anti-amyloid therapy.

There are currently no therapies that modify the course of AD, but several potential disease-modifying drug candidates are under investigation. These candidates include small molecules and immunotherapy (active and passive) that target the Aβ pathway and aim to provide therapeutic benefit by reducing either soluble or insoluble forms of Aβ in the brain and cerebrospinal fluid (CSF). Aducanumab is a human monoclonal antibody that recognizes aggregated forms of Aβ, including soluble Aβ oligomers and deposited fibrillar Aβ. Earlier publications have reported on results that demonstrated in the brain of an animal model of AD that both soluble oligomers and amyloid plaques are neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008] and clearance of amyloid plaques could lead to normalization of calcium homeostasis and neuronal activity, as well as reduction of oxidative stress [Rozkalne

2009; Spires-Jones 2009]. Similarly, patients with AD who generated anti-Aβ antibodies after active immunization with aggregated Aβ(42) showed slower rates of decline of cognitive function and activities of daily living [Hock 2003].

5.1. Profile of Previous Experience With Aducanumab

5.1.1. Nonclinical Experience

Aducanumab is a unique human, anti-Aβ immunoglobulin (Ig) G1 monoclonal antibody identified and derived from B lymphocytes using the reverse translational medicine approach. Using this technique, immune repertoires obtained from cohorts of healthy elderly human donors with excellent cognitive performance or with impaired but stable courses were screened for memory B cells against aggregated Aβ.

In vitro studies have demonstrated that aducanumab and its analogs are highly selective for soluble oligomeric and insoluble fibrillar forms of Aβ relative to soluble low-molecular-weight forms of Aβ. In vivo pharmacology studies indicated that a murine IgG2a chimeric version of the antibody (ch12F6A) with similar properties to aducanumab (BIIB037) significantly reduced amyloid plaque burden in the brains of aged Tg2576 mice, a mouse model of AD, through a microglia-mediated phagocytic mechanism. These data suggest aducanumab could provide benefit by reducing plaque burden.

The toxicokinetic profile of aducanumab was evaluated in Tg2576 mice in 13-week and 6-month studies and in cynomolgus monkeys in a 4-week study. Of the 2 species, the Tg2576 mouse is considered the primary pharmacologically relevant species given that these mice accumulate amyloid plaques in the cerebral parenchyma and vasculature. In addition to the standard histopathological evaluation in mice, Perls' staining of hemosiderin (a breakdown product of hemoglobin) was performed to quantify microhemorrhage. Microhemorrhage has been observed both as a background finding in transgenic mouse models of AD [Winkler 2001], including Tg2576 mice [Kumar-Singh 2005], and as a drug-related finding in transgenic mice treated with some anti-Aβ antibodies [Pfeifer 2002; Racke 2005; Wilcock and Colton 2009].

Findings consistent with amyloid plaques and vascular amyloid were identified in the brain sections of animals in all groups, including the control group, as expected with this model. In both studies, repeated administration of ch12F6A or aducanumab was well tolerated with no treatment-related deaths observed during the dosing period. In the 13-week toxicology study, meningeal/cerebral vascular inflammation and/or vascular thickening were observed in mice dosed with ch12F6A $\geq$ 70 mg/kg compared with the control group. In the 6-month study, although slight differences were observed between ch12F6A-treated groups and the control group, animals treated with aducanumab were comparable to the control animals. The evaluation of microhemorrhage, characterized by quantification of hemosiderin in Perls stained brain sections of each main study and recovery animal, demonstrated no significant increase in scores with ch12F6A or aducanumab treatment in either study. The incidence and severity of hemorrhage or cerebral vascular inflammation were comparable in the 13-week and 6-month mouse studies.

See the Investigator's Brochure (IB) for detailed information on nonclinical studies.

5.1.2. Clinical Experience

Aducanumab has been evaluated in one completed single ascending dose study (221AD101) and one ongoing multiple ascending dose study (221AD103):

- Study 221AD101 was a Phase 1, randomized, double-blind, placebo-controlled, study of aducanumab in subjects with mild or moderate AD.

  The primary objective was to evaluate the safety and tolerability of a range of aducanumab doses (0.3 to 60 mg/kg) when administered as single intravenous (IV) infusions. The secondary objectives were to assess the pharmacokinetic (PK) and immunogenicity of aducanumab after single-dose administration.

  A single dose of aducanumab up to 30 mg/kg was demonstrated to be well tolerated. Dose-limiting ARIA (2 subjects with ARIA-E [edema] and 1 subject with ARIA-E and ARIA-H [microhemorrhage]) was observed in the 60 mg/kg dose group resulting in termination of further dosing in that cohort; no cases of ARIA were observed at single doses below 60 mg/kg. The PK profile was dose linear.

- Study 221AD103 is an ongoing randomized, double-blind, placebo-controlled multiple dose study of aducanumab in subjects with prodromal or mild AD who are amyloid positive. The study comprises a placebo-controlled period with subjects receiving monthly doses of aducanumab (fixed doses of 1, 3, 6, or 10 mg/kg, or titration up to 10 mg/kg) or placebo for a year followed by a dose-blind long-term extension (LTE) period with subjects receiving monthly doses of aducanumab. Note: The fixed-dose cohorts enrolled both apolipoprotein E4 (ApoE ε4) carriers and non-carriers while the titration cohort is comprised of ApoE ε4 carriers only.

  The primary objective of Study 221AD103 is to evaluate the safety and tolerability of multiple doses of aducanumab administered monthly as single IV infusions. The secondary objectives are to assess the effect of aducanumab on cerebral amyloid plaque content as measured by ^{18}F-florbetapir positron emission tomography (PET), and to evaluate the PK and immunogenicity of aducanumab after multiple-dose administration. Exploratory objectives include assessment of the effect of aducanumab on the clinical progression of AD as measured by CDR-sum of boxes (SB) and MMSE.

  In the most recent interim analysis (25 May 2017), the incidence of ARIA has been observed to be both dose- and ApoE ε4 carriage-dependent, especially at the highest doses when administered as a fixed dose. ARIA-E was radiographically monitored by magnetic resonance imaging (MRI) and typically observed early in treatment (between 2 to 5 doses). In most cases, ARIA-E resolved 4 to 12 weeks after onset and ARIA-H was typically stable 2 to 4 weeks after onset. In the placebo-controlled period, the incidence of ARIA-E appeared to be lower in the group receiving titration to 10 mg/kg (comprising ApoE ε4 carriers only; 8/23 [35%]) than in carriers in the 6 mg/kg and 10 mg/kg fixed-dose groups (9/21 [43%] and 11/20 [55%], respectively). Of note, among the subjects receiving titration to 10 mg/kg who had ARIA-E, the abnormalities were observed at the 3 and 6 mg/kg dose levels, before they reached

10 mg/kg. Also, 13 (of 23, 57%) subjects in the titration arm have been titrated to 10 mg/kg, and of these, 12 continued treatment and received at least 17 doses of 10 mg/kg; none of these subjects experienced ARIA-E or ARIA-H. Furthermore, ARIA-E events when they occurred (in the titration group) have been either asymptomatic or associated with mild symptoms that resolved, and most subjects who had ARIA-E continued treatment (6/8; 75%) compared with only 36% (4/11) of carriers in the fixed-dose 10 mg/kg arm (refer to the IB for details on events of ARIA). In the LTE period, the incidence of ARIA-E in ApoE ε4 carriers who were titrated up to 6 mg/kg (2 doses of 3 mg/kg, then 6 mg/kg) was 23% (3/13), with an overall rate of 16% (3/19) as no ApoE ε4 non-carriers (0/6) experienced ARIA-E.

Protocol-specified interim analyses of the ongoing multiple-ascending dose Study 221AD103 have demonstrated engagement of aducanumab with amyloid plaques, a pharmacodynamic (PD) effect on amyloid reduction, and an effect on CDR-SB and MMSE suggestive of a slowing of clinical decline in aducanumab-treated subjects. The dose- and time-dependent reduction of brain Aβ burden observed with aducanumab treatment was statistically significant at doses of 3, 6, and 10 mg/kg after 6 and 12 months of dosing, as well as with 1 mg/kg and titration from 1 to 10 mg/kg after 12 months of dosing. Further dose-dependent reductions in brain Aβ were observed for up to 36 months. Subjects who switched from placebo to aducanumab in the LTE period saw a reduction in brain Aβ similar to that seen by subjects who received aducanumab in the placebo-controlled period. The results demonstrate target engagement (amyloid plaques) and a PD effect (dose-dependent amyloid reduction).

In addition, results from the interim analyses showed an effect at 1 year on the exploratory endpoints CDR-SB and MMSE (at fixed doses of 1 mg/kg, 3 mg/kg, 6 mg/kg and 10 mg/kg compared with placebo), suggesting a reduction in the progression of clinical impairment for aducanumab-treated versus placebo-treated subjects. Furthermore, generally consistent treatment differences were seen for the fixed-dose cohorts, and in the titration group, effects on the CDR-SB and MMSE after 1 year were generally consistent with the fixed-dose results. Compared with placebo, adjusted mean changes from baseline to Week 54 in CDR-SB scores favored all aducanumab dose regimens tested, with treatment differences of 0.5 points or greater favoring aducanumab at doses of 3, 6, and 10 mg/kg and titration to 10 mg/kg, and statistical significance seen in the 10 mg/kg and titration groups. On the MMSE, adjusted mean decreases from baseline to Week 52 suggested a clinically meaningful benefit in the 3 and 10 mg/kg groups and the titration group and were significantly lower than placebo in the 10 mg/kg group. Furthermore, CDR-SB and MMSE data suggested a clinical benefit in those continuing on aducanumab up to 3 years compared with those who switched from placebo to aducanumab in the LTE period. Refer to the IB for details on interim analyses results.

5.2. Study Rationale

The purpose of this study is to assess the efficacy and safety of aducanumab compared with placebo in subjects with early AD including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD. Aducanumab is a human IgG1 monoclonal antibody that recognizes aggregated forms of Aβ, including soluble Aβ oligomers and deposited fibrillar Aβ. Earlier publications have demonstrated that both soluble oligomers and amyloid plaques are neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008] and clearance of amyloid plaques could lead to normalization of calcium homeostasis and neuronal activity, as well as reduction of oxidative stress in the brain of an animal model of AD [Rozkalne 2009; Spires-Jones 2009]. For this reason, treatment with aducanumab is expected to slow progression of AD, while preserving global function longer, when compared with untreated subjects.

Interim analyses of the ongoing multiple dose study (Study 221AD103) have demonstrated target engagement, a PD effect on amyloid reduction, and an effect on CDR-SB and MMSE suggestive of a reduction in the progression of clinical impairment for aducanumab-treated subjects. These results, along with the observed safety and tolerability profile, warrant the further Phase 3 investigation of aducanumab in a patient population spanning the early stages of the AD continuum.

5.3. Rationale for Dose and Schedule Selection

The dosing regimen selected for this study was based on the PK and PD relationship for removal of brain amyloid and effect on CDR-SB and MMSE observed in Study 221AD103 interim analyses and on safety, tolerability, and PK data from studies 221AD101 (complete) and 221AD103 (ongoing).

The dose- and time-dependent reduction of brain amyloid burden observed with aducanumab treatment in Study 221AD103 was statistically significant at doses of 3, 6, and 10 mg/kg after 6 months of dosing, and at 3, 6, and 10 mg/kg as well as with titration to 10 mg/kg after 12 months of dosing. On the exploratory endpoints of CDR-SB and MMSE changes from baseline, a dose-dependent slowing of clinical decline was observed for aducanumab versus placebo after 1 year of treatment. Compared with placebo, adjusted mean changes from baseline to Week 54 for CDR-SB favored all the aducanumab dose groups tested, with treatment differences of 0.5 points or greater at fixed doses of aducanumab 3, 6, and 10 mg/kg and also with titration to 10 mg/kg. On the MMSE, adjusted mean decreases from baseline to Week 52 were smaller in all dose groups than in the placebo group. Of note, on the CDR-SB, the point estimate for the titration group (comprising ApoE ε4 carriers only) was generally similar to that for the 10 mg/kg group and significantly lower than placebo in both those groups; on the MMSE, the point estimate for the titration group is generally similar to that in the 10 mg/kg group (which showed significantly less decline than placebo) and the 3 mg/kg group.

In the most recent interim analysis (25 May 2017), the incidence of ARIA has been observed to be both dose- and ApoE ε4 carriage-dependent, especially at the highest doses when administered as a fixed dose. However, the incidence of ARIA-E, as well as discontinuations from treatment due to ARIA-E, in subjects receiving aducanumab titrated to 10 mg/kg (ApoE ε4 carriers only) appear to be reduced (8/23 [35%]) compared with fixed doses of aducanumab at

6 mg/kg (9/21 [43%]) and 10 mg/kg (11/20 [55%]). Furthermore, among those subjects randomized to receive aducanumab titrated to 10 mg/kg, ARIA-E occurred only at the 3 mg/kg and 6 mg/kg dose levels. Also, 13 (of 23, 57%) subjects in the titration arm have been titrated to 10 mg/kg, and of these, 12 continued treatment and received at least 17 doses of 10 mg/kg; none of these subjects experienced ARIA-E or ARIA-H.

In an effort to maximize the dose-dependent amyloid reduction and effect on CDR-SB and MMSE that have been observed with doses of 3 mg/kg and higher while maintaining ARIA incidence, severity, and related discontinuation rate within acceptable levels, a titration regimen will be explored in this study. It has been suggested that the ARIA observed following treatment with amyloid targeting agents may be due, in part, to the initial large removal of amyloid and subsequent saturation of perivascular brain amyloid clearance mechanisms [Weller 2008]. Titration to the target dose is expected to result in slower initial amyloid removal, yet trigger alternative mechanisms of amyloid clearance including monoclonal antibody-dependent Fc-mediated microglial clearance [Ostrowitzki 2012], which would prevent saturation of amyloid clearance and subsequent ARIA during titration and once the target dose is reached. Since aducanumab-induced ARIA has been demonstrated to occur early during treatment, with most cases occurring within the first 5 doses, titration of aducanumab for up to 6 doses prior to reaching the target dose may result in reduction of ARIA incidence and severity.

Given the tolerability and apparent efficacy of aducanumab shown, the doses to be tested using a titration regimen are 3 and 10 mg/kg for ApoE ε4 carriers, and 6 and 10 mg/kg for ApoE ε4 non-carriers. Titration will start at 1 mg/kg and will escalate to 3, 6, and 10 mg/kg as detailed below.

5.3.1. Dosing Scheme

5.3.1.1. Placebo-Controlled Period

Doses will be administered approximately 4 weeks apart, over approximately 76 weeks (a total of 20 doses). Based upon their ApoE ε4 carrier status, subjects will be assigned to 1 of 3 treatment groups (approximately 535 subjects each [see Section 16.8]) in a 1:1:1 ratio (aducanumab low dose:aducanumab high dose:placebo) as follows (Table 12 and Figure 1):

ApoE ε4 Carrier

- Low dose (3 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg thereafter

- High dose (10 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter

- Placebo

  Saline infusion

ApoE ε4 Non-Carrier

- Low dose (6 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 4 doses, and 6 mg/kg thereafter

- High dose (10 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter

- Placebo

  Saline infusion

Table 12: Dosing Scheme for Aducanumab by Treatment Group and ApoE ε4 Carrier Status

Dose (Month)		1	2	3	4	5	6	7 to 20
Treatment Group		Dose (mg/kg)						
ApoE ε4 (+)	Low Dose	1	1	3	3	3	3	3
	High Dose	1	1	3	3	6	6	10[1]
	Placebo	saline						
ApoE ε4 (-)	Low Dose	1	1	3	3	3	3	6
	High Dose	1	1	3	3	6	6	10
	Placebo	saline						

[1] 10 mg/kg is the target dose for all ApoE ε4 carriers assigned to the aducanumab high-dose group. Subjects enrolled under protocol versions prior to Version 4 and assigned to the previous high-dose of 6 mg/kg will be titrated to 10 mg/kg upon receipt of at least 2 doses at 6 mg/kg.

5.3.2. Dosing Scheme Modification

An independent data monitoring committee (IDMC) will review unblinded safety data, including serious AEs (SAEs) and incident cases of ARIA, from all ongoing aducanumab studies (e.g., Studies 221AD103, 221AD104, 221AD301, and 221AD302) as described in the IDMC charter.

The dosing scheme can be modified in the following circumstances:

- Safety and tolerability of the high dose

  If the high dose (10 mg/kg) is deemed not acceptable, enrollment for the high-dose group(s) will be terminated and subjects will not be replaced. Subjects who have already been randomized to the discontinued dose will be down-dosed to the next available dose according to their ApoE ε4 carrier status. Definition of low and high-dose groups will be revised as described in Section 16.

5.3.3. Long-Term Extension Period

Subjects who received aducanumab in the placebo-controlled period and who enter the LTE period will maintain the dosing scheme outlined in the protocol at the time of transition from the placebo-controlled period to the LTE period (e.g., subjects who are on stable dosing in the placebo-controlled period will continue on the same dose, subjects who are on a titration regimen during the transition will continue to titrate into the LTE period and subjects who complete the placebo-controlled period under protocol versions prior to Version 4 and are assigned to the high dose aducanumab treatment group may up titrate to 10 mg/kg in the LTE). Subjects randomized to placebo at the start of the placebo-controlled period (Study Day 1) will also be randomized to receive dose-blinded aducanumab (low dose:high dose, 1:1 ratio) for the LTE period. Randomization will be stratified by subject ApoE ε4 carrier status. Subjects will be dosed using the same regimen described for the placebo-controlled period (see Table 12 and Figure 1).

Any modifications to the dosing scheme (i.e., termination of high-dose group, as described in Section 5.3.2) will also be implemented in the LTE period.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

The primary objective of the study is to evaluate the efficacy of monthly doses of aducanumab in slowing cognitive and functional impairment as measured by changes in the CDR-SB score as compared with placebo in subjects with early AD.

The primary endpoint that relates to this objective is change from baseline in CDR-SB score at Week 78.

6.2. Secondary Objectives and Endpoints

A secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by the MMSE.

- The endpoint that relates to this objective is change from baseline in MMSE score at Week 78.

Another secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by ADAS-Cog 13.

- The endpoint that relates to this objective is change from baseline in ADAS-Cog 13 score at Week 78.

Another secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by ADCS-ADL-MCI.

- The endpoint that relates to this objective is change from baseline in ADCS-ADL-MCI score at Week 78.

6.3. Tertiary Objectives and Endpoints

6.3.1. Tertiary Objectives

Safety and Tolerability

- To assess the safety and tolerability of monthly doses of aducanumab.
- To assess the immunogenicity of aducanumab.

Biomarker/Efficacy/Health Outcomes

- To assess the effect of aducanumab on cerebral amyloid plaque content as measured by amyloid PET imaging (in a subset of approximately 400 subjects).
- To assess the effect of aducanumab on behavior as measured by the Neuropsychiatric Inventory-10 (NPI-10).
- To assess the effect of aducanumab on subject health status, measured by EuroQol health status measures (EQ-5D [informant-rated and subject self-reported]).

- To assess the effect of aducanumab on subject self-reported cognitive function, measured by the modified Perceived Deficits Questionnaire-20 (mPDQ-20) [Lenderking 2014].
- To assess the correlation between primary endpoint and cerebral amyloid plaque content as measured by PET imaging.

Pharmacokinetics

- To collect and characterize the PK parameters of aducanumab in serum.

6.3.2. Tertiary Endpoints

Safety and Tolerability

- Incidence of all AEs and SAEs.
- Brain MRI findings including incidence of ARIA-E and ARIA-H.
- Clinical laboratory shifts in reported values.
- Clinically significant changes in vital sign measurements and electrocardiograms (ECGs).
- Incidence of anti-aducanumab antibodies in serum.

Biomarkers/Efficacy/Health Outcomes

- Change from baseline in amyloid PET signal at Week 26 (in a subset of sites and subjects).
- Change from baseline in amyloid PET signal at Week 78 (in a subset of sites and subjects).
- Change from baseline in NPI-10 score at Week 78.
- Change from baseline in subject self-reported EQ-5D index score at Week 78.
- Change from baseline in informant-rated subject EQ-5D index score at Week 78.
- Change from baseline in mPDQ-20 at Week 78.
- Correlation between the primary endpoint and cerebral amyloid plaque content as measured by PET imaging over time.

Pharmacokinetics

- Serum concentrations and PK parameters of aducanumab.

6.4. Additional Exploratory Objectives and Endpoints

6.4.1. Additional Exploratory Objectives

Biomarkers

- To assess the effect of aducanumab on various morphometric measures in certain brain areas as measured by MRI.
- To assess the effect of aducanumab on functional connectivity by task-free functional MRI (tf-fMRI) [where available, in a subset of sites and subjects].
- To assess the effect of aducanumab on cerebral blood flow by arterial spin labeling (ASL)-MRI (where available, in a subset of sites and subjects).
- To assess the effect of aducanumab on disease- or treatment-related biomarkers in CSF, which may include, but are not limited to, amyloid and tau proteins (in a subset of subjects).
- To assess the effect of aducanumab on disease- or treatment-related biomarkers in blood, which may include, but are not limited to, amyloid and tau proteins.
- To assess the effect of aducanumab on tau pathology by tau PET imaging (where available, in a subset of sites and subjects).

Health Outcomes

- To assess the effect of aducanumab on the informant/care partner's own health status, measured by the EQ-5D.
- To assess the effect of aducanumab on caregiver burden as measured by the Caregiver Assessment Measure (CAM).

6.4.2. Additional Exploratory Endpoints

Biomarkers

- Change from baseline in whole brain volume, hippocampal volume, ventricular volume, and cortical gray matter volume measured by MRI over time.
- Change from baseline in functional connectivity as measured by tf-fMRI over time (where available, in a subset of sites and subjects).
- Change from baseline in cerebral blood flow as measured by ASL-MRI over time (where available, in a subset of sites and subjects).
- Change from baseline in CSF biomarkers, which may include, but are not limited to, amyloid or tau proteins at Week 78 (in a subset of subjects).
- Change from baseline over time in blood biomarkers, which may include, but are not limited to, amyloid or tau proteins.
- Change from baseline in tau PET signal at Week 78 (where available, in a subset of sites and subjects).

Health Outcomes

- Change from baseline in informant/care partner's own EQ-5D index-score at Week 78.

- Changes on the CAM over time.

6.5. Long-Term Extension Objectives and Endpoints

6.5.1. Tertiary LTE Objectives

- To evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD.
- To evaluate the long-term efficacy of aducanumab treatment as measured by clinical, radiological, and health outcomes assessments.

6.5.2. Tertiary LTE Endpoints

- The incidence of AEs and/SAEs; brain MRI findings (including the incidence of ARIA-E and ARIA-H); and the incidence of anti-aducanumab antibodies in serum over the placebo-controlled and LTE periods of the study.
- Change in the following measures over the placebo-controlled and LTE periods of the study:
  - CDR-SB score.
  - MMSE score.
  - ADAS-Cog 13 score.
  - ADCS-ADL-MCI score.
  - Amyloid PET signal (in a subset of sites and subjects).
  - NPI-10 total score.
  - Informant-rated EQ-5D index score.

6.5.3. Additional Exploratory LTE Objective

- To evaluate the long-term efficacy of aducanumab treatment as measured by radiological, clinical, and additional health outcomes.

6.5.4. Additional Exploratory LTE Endpoints

- Change in the following measures over the placebo-controlled and LTE periods of the study:
  - Whole brain volume, hippocampal volume, ventricular volume, and cortical gray matter volume measured by MRI.
  - Functional connectivity as measured by tf-fMRI (where available, in a subset of sites and subjects).
  - Cerebral blood flow as measured by ASL-MRI (where available, in a subset of sites and subjects).

- Disease- or treatment-related biomarkers levels in CSF, which may include, but are not limited to, amyloid and tau proteins (in a subset of subjects).
- Disease- or treatment-related biomarker levels in blood, which may include, but are not limited to, amyloid and tau proteins.
- Informant/care partner's own self-reported EQ-5D index score.
- CAM.
- Tau PET signal (where available, in a subset of sites and subjects).

7. STUDY DESIGN

7.1. Study Overview

Study 221AD302 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 study in subjects with early AD, including MCI due to AD and a subset of mild AD, followed by an optional dose-blinded LTE period of up to 5 years. Approximately 1605 subjects (see Section 16.8) will be enrolled across approximately 150 centers globally. The primary study objective is to evaluate the efficacy of monthly doses of aducanumab on the CDR-SB relative to placebo. Secondary objectives include assessment of the effect of monthly doses of aducanumab on clinical progression as compared to placebo. The safety of monthly doses of aducanumab will also be evaluated.

Subjects will receive infusions of aducanumab or placebo approximately every 4 weeks for approximately 18 months (a total of 20 doses). Subjects will be randomized to receive aducanumab low dose:aducanumab high dose:placebo in a 1:1:1 ratio. The randomization will be stratified by site and ApoE ε4 status (carrier or non-carrier). The ratio of ApoE ε4 carriers to non-carriers in the study population will generally reflect the distribution in the broader AD population. Enrollment will also be monitored, via interactive response technology (IRT), such that subjects with mild AD represent a small percentage of the total enrolled in the trial.

At the end of the double-blind, placebo-controlled treatment period, subjects who meet the extension entry criteria may enter a long-term safety and efficacy extension period, with all subjects receiving aducanumab approximately every 4 weeks (up to a total of 65 doses over 5 years). The EOT Visit will occur at Week 338, or when the last subject has had his or her Week 182 Visit, whichever occurs first.

The total duration of study participation for each subject only participating in the placebo-controlled period of the study will be up to approximately 102 weeks, including a series of screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, and a safety follow-up (FU) period of 18 weeks after the final dose.

The total duration of study participation for each subject participating in the placebo-controlled period and the LTE period will vary and be up to approximately 362 weeks, including a series of screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, a 4-week FU period, a 256-week aducanumab dose-blind treatment period, and a safety FU period of 18 weeks after the final dose. The FU period of 18 weeks is based on an estimated mean elimination half-life in humans of 16 to 24 days (mean approximately 20 days, based on results from the single ascending dose study [Study 221AD101]) and anticipated brain concentrations of aducanumab of less than one-third the EC_{50} (inhibitory concentration at 50% of the maximum observed biologic effect) for binding fibrillar amyloid at 8 weeks after the last dose.

During the placebo-controlled period, ApoE ε4 carriers will receive placebo, aducanumab 3 mg/kg, or aducanumab 10 mg/kg whereas ApoE ε4 non-carriers will receive

placebo, aducanumab 6 mg/kg, or aducanumab 10 mg/kg. Aducanumab will be titrated for up to 6 doses prior to reaching the target dose as shown in Table 12 and Figure 1. Note: As of Protocol Version 4, 10 mg/kg is the target dose for all ApoE ε4 carriers in the high-dose group. ApoE ε4 carriers who were randomly assigned to the high-dose group when the target dose was 6 mg/kg (under protocol versions prior to Version 4) must have received 2 or more doses at 6 mg/kg prior to being titrated up to 10 mg/kg. Subjects who received placebo during the placebo-controlled period will be assigned to treatment based upon their ApoE ε4 carrier status in a 1:1 ratio (aducanumab low dose:aducanumab high dose) for the LTE period, and aducanumab will be titrated for up to 6 doses prior to reaching the target dose following the same schedule described for the placebo-controlled period.

See Section 5.3.2 for details of dosing scheme modification.

Individual dose adjustments may also be implemented in subjects who develop ARIA. See Section 7.2.1.

Investigators, study site staff (except for the designated unblinded pharmacist/technician), and study subjects will be blinded to the subjects' randomized treatment assignment for the placebo-controlled period. During the LTE period, Investigators and subjects will remain blinded to the treatment assignment in the placebo-controlled period and the aducanumab dose for the LTE period.

7.2. Study Specifics

7.2.1. Dose Suspension, Modification, or Termination for ARIA Events

Discontinuation of Dosing for a Given Subject

The central MRI reading center will report incident cases of ARIA-E and ARIA-H to both the Sponsor and the PI within a specified time after observing the finding on MRI per the imaging manual procedures. All cases of ARIA will be reviewed by the Sponsor and the PI; decisions on dosing continuation, interruption, or discontinuation will be based on clinical symptoms, and the MRI information provided by the central reader. IDMC notification rules will be outlined in the IDMC charter. Guidelines on the management and disposition of ARIA-E and ARIA-H cases (including the criteria to be met for the continuation, suspension/resumption, permanent discontinuation of dosing due to ARIA, resumption of dosing after dose suspension due to ARIA [including rules for titrating up to the assigned dose], and management of recurrent ARIA) are provided in the following subsections. Dosing may also be terminated at the discretion of the Sponsor for medical reasons. See Section 10.1 for the full list of criteria for discontinuing study treatment.

7.2.1.1. ARIA-E Cases

Table 13: Disposition of ARIA-E Cases

<table>
<tr><th rowspan="2">Clinical Symptom Severity</th><th colspan="3">ARIA-E Severity on MRI (Central Read)</th></tr>
<tr><th>Mild</th><th>Moderate</th><th>Severe</th></tr>
<tr><td>Asymptomatic</td><td>Continue dosing at current dose and schedule</td><td colspan="2">Suspend dosing. Once ARIA-E resolves the subject may resume dosing at the same dose.</td></tr>
<tr><td>Mild</td><td colspan="3" rowspan="4">Suspend dosing. Once ARIA-E and clinical symptoms resolve, the subject may resume dosing at the same dose.</td></tr>
<tr><td>Moderate</td></tr>
<tr><td>Severe</td></tr>
<tr><td>Serious "other medically important event" only[1]</td></tr>
<tr><td>Serious, except for "other medically important event"[2]</td><td colspan="3">Discontinue Dosing</td></tr>
</table>

[1] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above and as described in Section 15.1.2.

[2] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.1.2.

- Subjects who develop **mild ARIA-E, per central MRI reading, with no clinical symptoms** at any time during the study may continue in the study at their current dose. Subjects should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-E has resolved per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. The Sponsor may require that the subjects discontinue dosing or continue dosing at a lower dose level based on review of safety and MRI data.
- Subjects who develop **moderate or severe ARIA-E, per central MRI reading, with no clinical symptoms** at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-E has resolved per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. If the ARIA-E has resolved and the subjects remain asymptomatic (in the Investigator's opinion), the subjects may resume treatment at the same dose.

- Subjects who develop **mild, moderate, or severe ARIA-E, per central MRI reading, accompanied by mild, moderate, severe, or serious ("other medically important event" only) clinical symptoms** at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-E has resolved per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. If the ARIA-E has resolved and the clinical symptoms have resolved (in the Investigator's opinion), the subject may resume treatment at the same dose.
- Subjects who develop mild, moderate, or severe ARIA-E, per central MRI reading, accompanied by serious (except "other medically important event") clinical symptoms at any time during the study will permanently discontinue treatment but remain in study. Subjects should complete a FU Visit 18 weeks after the final dose, protocol-required tests and assessments at a subset of the clinic visits (see Table 10, and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-E has resolved per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.

See Section 7.2.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.1.2. ARIA-H (Microhemorrhage)

In this study, new incident microhemorrhages are defined as new incident microhemorrhages that occur on treatment and do not include microhemorrhages at baseline.

Table 14: Disposition of ARIA-H (Microhemorrhage) Cases

<table>
<tr><th rowspan="3">Clinical Symptom Severity</th><th colspan="3">New Incident Microhemorrhages[1] (Central Read)</th></tr>
<tr><th>Mild</th><th>Moderate</th><th>Severe</th></tr>
<tr><th>≥ 1 and ≤ 4</th><th>≥ 5 and ≤ 9</th><th>≥ 10</th></tr>
<tr><td>Asymptomatic</td><td>Continue dosing at current dose and schedule</td><td>Suspend dosing. Once ARIA-H is stable, the subject may resume dosing at the same dose.</td><td rowspan="5">Discontinue dosing</td></tr>
<tr><td>Mild</td><td colspan="2" rowspan="4">Suspend dosing. Once ARIA-H stabilizes and clinical symptoms resolve, the subject may resume dosing at the same dose.</td></tr>
<tr><td>Moderate</td></tr>
<tr><td>Severe</td></tr>
<tr><td>Serious "other medically important event" only[2]</td></tr>
<tr><td>Serious, except for "other medically important event"[3]</td><td colspan="2">Discontinue dosing</td></tr>
</table>

[1] New incident microhemorrhages = new incident microhemorrhages on treatment; does not include microhemorrhages at baseline.

[2] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above as described in Section 15.1.2.

[3] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.1.2.

Asymptomatic ARIA-H (Microhemorrhage)

- Subjects who develop a **≥ 1 and ≤ 4 new incident microhemorrhage(s) [mild]** at any time during the study may continue treatment at the current dose.
- Subjects who develop **≥ 5 and ≤ 9 new incident microhemorrhages [moderate]** occurring at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the microhemorrhage is confirmed as stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. A microhemorrhage is considered stable if there is no change or a decrease in the number, size, severity, or number of locations between 2 consecutive MRIs including the initial detection MRI and the MRI performed 4 weeks (±5 days) later. Once the microhemorrhage is deemed stable, subjects may resume treatment at the same dose.

- Subjects who develop **≥ 10 new incident microhemorrhages [severe]** during the study will permanently discontinue treatment but remain in study. Subjects should complete a FU Visit 18 weeks after the final dose, protocol-required tests and assessments at a subset of the clinic visits (see Table 10 and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the microhemorrhages are deemed stable per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.

Symptomatic ARIA-H (Microhemorrhage)

- Subjects who develop **≤ 9 new incident microhemorrhages (mild or moderate) and mild, moderate, severe, or serious ("other medically important event" only [Section 15.1.2]) clinical symptoms** will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-H (microhemorrhage(s) is confirmed stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. Microhemorrhages are considered stable if there is no change or a decrease in the number, size, severity, or number of locations between 2 consecutive MRIs including the initial detection MRI and the MRI performed 4 weeks (±5 days) later. Once ARIA-H (microhemorrhage) is deemed stable and the clinical symptoms have resolved (in the Investigator's opinion), the subject may resume treatment at the same dose.
- Subjects who experience **serious (except "other medically important event" [Section 15.1.2]) clinical symptoms associated with microhemorrhage(s)** will permanently discontinue treatment but remain in study. Subjects should complete a FU Visit 18 weeks after the final dose, protocol-required tests and assessments at a subset of the clinic visits (see Table 10 and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the microhemorrhage(s) is confirmed stable per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.
- Subjects who develop **≥ 10 new incident microhemorrhages (severe)**, regardless of symptom severity, during the study will permanently discontinue treatment but remain in study. Subjects should complete a FU Visit 18 weeks after the final dose, protocol-required tests and assessments at a subset of the clinic visits (see Table 10 and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the microhemorrhages are deemed stable per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.

See Section 7.2.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.1.3. ARIA-H (Superficial Siderosis)

Table 15: Disposition of ARIA-H (Superficial Siderosis) Cases

<table>
<tr><td rowspan="2">Clinical Symptom Severity</td><td colspan="3">New Incident Areas of Superficial Siderosis[1] (Central Read)</td></tr>
<tr><td>Mild</td><td>Moderate</td><td>Severe</td></tr>
<tr><td></td><td>1</td><td>2</td><td>>2</td></tr>
<tr><td>Asymptomatic</td><td>Continue dosing at current dose and schedule</td><td>Suspend dosing. Once ARIA-H is stable the subject may resume dosing at the same dose.</td><td rowspan="5">Discontinue dosing</td></tr>
<tr><td>Mild</td><td colspan="2" rowspan="4">Suspend dosing. Once ARIA-H stabilizes and clinical symptoms resolve, the subject may resume dosing at the same dose.</td></tr>
<tr><td>Moderate</td></tr>
<tr><td>Severe</td></tr>
<tr><td>Serious "other medically important event" only[2]</td></tr>
<tr><td>Serious, except for "other medically important event"[3]</td><td colspan="2">Discontinue dosing</td></tr>
</table>

[1] New incident superficial siderosis = new incident superficial siderosis on treatment.

[2] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above as described in Section 15.1.2.

[3] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.1.2.

Asymptomatic ARIA-H (Superficial Siderosis)

- Subjects who develop a **single incident focal area of hemosiderosis (also referred to as superficial siderosis) [mild]** may continue treatment at the current dose, but must have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the superficial siderosis is confirmed as stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. Superficial siderosis is considered stable if there is no change or a decrease in the number, size, severity, or number of locations between 2 consecutive MRIs, including the initial detection MRI and the MRI performed 4 weeks (±5 days) later.
- Subjects who develop **2 focal areas of hemosiderosis (superficial siderosis) [moderate]** occurring at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in

addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-H (superficial siderosis) is confirmed as stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. Once the superficial siderosis is deemed stable, the subjects may resume treatment at the same dose.

- Subjects who develop >**2 focal areas of hemosiderosis (superficial siderosis) [severe]** occurring at any time during the study must permanently discontinue treatment but remain in study. Subjects should complete a FU Visit 18 weeks after the final dose, protocol-required tests and assessments at a subset of the clinic visits (see Table 10 and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-H (superficial siderosis) is confirmed as stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.

Symptomatic ARIA-H (superficial siderosis)

- Subjects who develop **≤ 2 new focal areas of superficial siderosis (mild or moderate)** and **mild, moderate, severe, or serious ("other medically important event" only)** clinical symptoms will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-H superficial siderosis is confirmed stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. Superficial siderosis is considered stable if there is no change or a decrease in the number, size, severity, or number of locations between 2 consecutive MRIs including the initial detection MRI and the MRI performed 4 weeks (±5 days) later. Once the ARIA-H (superficial siderosis) is deemed stable and the clinical symptoms have resolved (in the Investigator's opinion), the subjects may resume treatment at the same dose.
- Subjects who experience **serious (except "other medically important event" [Section 15.1.2]) clinical symptoms associated with ARIA-H (superficial siderosis)** will permanently discontinue treatment but remain in study. Subjects should complete a FU Visit 18 weeks after the final dose, protocol-required tests and assessments at a subset of the clinic visits (see Table 10 and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the superficial siderosis is confirmed stable per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.
- Subjects who develop **>2 new focal areas of superficial siderosis (severe)** regardless of clinical symptom severity will permanently discontinue treatment but remain in study. Subjects should complete a FU Visit 18 weeks after the final dose, protocol-required tests and assessments at a subset of the clinic visits (see Table 10 and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA

every 4 weeks (±5 days) until the superficial siderosis is confirmed stable per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.

See Section 7.2.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.1.4. ARIA-H (Macrohemorrhage)

Subjects who develop any new incident macrohemorrhage (defined as >1 cm in diameter on T2* sequence), regardless of symptom severity during the study, will permanently discontinue treatment, but remain in study. Subjects should complete a FU Visit 18 weeks after the final dose, protocol-required tests and assessments at a subset of the clinic visits (see Table 10 and Table 11) and, in addition, have an unscheduled visit for MRI and MOCA every 4 weeks (±5 days) until the macrohemorrhage is confirmed stable per centrally read MRI. A macrohemorrhage is considered stable if there is no change or a decrease in the number, size, severity, or number of locations between 2 consecutive MRIs, including the initial detection MRI and the MRI performed 4 weeks (±5 days) later. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA-H (macrohemorrhage).

7.2.1.5. Coincident ARIA-H and ARIA-E Cases

Subjects who develop ARIA-H coincident with ARIA-E at any time during the study will follow the most restrictive guidelines. Prior to resuming treatment, where applicable, ARIA-E must resolve, ARIA-H must be deemed stable, and the subject must be asymptomatic. For example, if a subject experiences asymptomatic ARIA-H (1-4 microhemorrhages) coincident with ARIA-E assessed as moderate on MRI and accompanied by mild clinical symptoms, the dose should be suspended per the ARIA-E guidelines summarized in Table 13. In addition, unscheduled visits should occur as described in Section 7.2.1.1 through Section 7.2.1.4.

7.2.1.6. Resumption of Study Treatment After Suspension due to ARIA

7.2.1.6.1. MRI Monitoring

When treatment resumes after a dose suspension due to ARIA, an MRI and MOCA will be performed 2 weeks (±5 days) after the second administration of the restarted dose. In addition, if treatment was suspended during the dose titration prior to the subject reaching the maximum assigned dose, an MRI and MOCA will be performed 2 weeks (±5 days) after every second dose until completion of the titration period, with subjects assumed to be titrating to 10 mg/kg (titration period of 6 doses and a final MRI after the second dose at 10 mg/kg) to maintain study blinding, not counting unscheduled MRI visits for monitoring of ARIA. MRIs will otherwise be performed as indicated in the Schedule of Events (Section 4.2).

7.2.1.6.2. Dosing Upon Resumption of Study Treatment

Subjects who suspend treatment due to ARIA may resume treatment at the same dose if they meet the criteria as described in Sections 7.2.1.1 to 7.2.1.5. Subjects who suspend and then resume dosing after having already reached their assigned top dose level are to continue dosing at that dose level. However, if dosing is suspended prior to a subject reaching their assigned top dose level, the subject (1) must receive at least 2 doses at the restart dose before titrating up to the next dose level and (2) must complete at least the required number of doses at that dose level per their assigned treatment group, as outlined in the right column of Table 16.

Table 16: Resumption of Study Treatment Following Dose Suspension Due to ARIA During Titration

Assigned Treatment Group (Maximum Dose)	Dose Level at Which ARIA Occurred	Number of Doses Prior to ARIA	Number of Doses at Current Dose Level Needed Before Going to the Next Higher Dose
ApoE ε4 (+)			
Low Dose (3 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
High Dose (10 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	2
	3 mg/kg	2	2
	6 mg/kg	1	2
	6 mg/kg	2	2
ApoE ε4 (-)			
Low Dose (6 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	3
	3 mg/kg	2	2
	3 mg/kg	3	2
	3 mg/kg	4	2
High Dose (10 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	2
	3 mg/kg	2	2

Assigned Treatment Group (Maximum Dose)	Dose Level at Which ARIA Occurred	Number of Doses Prior to ARIA	Number of Doses at Current Dose Level Needed Before Going to the Next Higher Dose
	6 mg/kg	1	2
	6 mg/kg	2	2

7.2.1.7. Management After Recurrent ARIA (Dosing and MRI)

If the subject has more than one occurrence of ARIA (i.e., a second or any additional occurrences of ARIA-E or of ARIA-H, or ARIA-E and ARIA-H) that requires dose suspension (per criteria in Section 7.2.1.1, Section 7.2.1.2, and Section 7.2.1.3), after the ARIA resolves or stabilizes, the subject is to resume dosing at the same dose as that described in Section 7.2.1.6.2. Once dosing has resumed, the guidelines outlined in Table 16 apply. If a subject resumes treatment after ARIA, an MRI and MOCA will be performed 2 weeks (±5 days) after the second administration of the restarted dose, and 2 weeks (±5 days) after every second dose until the completion of titration, with all subjects assumed to be titrating to 10 mg/kg (6 doses) to maintain study blinding. MRIs will otherwise be performed as indicated in the Schedule of Events (Section 4.2).

Subjects who develop ARIA during the placebo-controlled period but continue or resume treatment at an active dose are eligible to enter the LTE period and will maintain the dosing scheme from the placebo-controlled period into the LTE, which may include a continuation on the same dose or completion of titration into the LTE period.

For subjects who discontinued treatment due to a third ARIA event that required dose suspension under a previous version of the protocol and remained on the study: these subjects will not resume dosing.

For subjects who resumed dosing at the next lower dose after recurrent ARIA under a previous version of the protocol and have not titrated to their target dose: these subjects will continue dosing (i.e., receive 2 doses at that dose level before titrating up to the next higher dose).

For subjects who dose-reduced to placebo after recurrent ARIA under a previous version of the protocol and remained in the study: these subjects can resume dosing during the LTE period and will be titrated up to his or her randomly assigned dose using the same regimen as that described for the placebo controlled period (see Table 12 and Figure 1).

For subjects who dose-reduced to placebo after recurrent ARIA and then resumed dosing at aducanumab 1 mg/kg during the LTE period under a previous version of the protocol: these subjects can be titrated up to his or her randomly assigned dose using the same regimen as that described for the placebo-controlled period (see Table 12 and Figure 1).

For subjects who had dose suspension due to a recurrent ARIA event prior to the implementation of Protocol Version 6.0 that did not resolve or stabilize until after the implementation of Protocol Version 6.0: these subjects are to resume dosing at the same dose as that described in Section 7.2.1.6.2.

7.2.2. Infusion Interruption

If any mild or moderate infusion-related reactions (e.g., headache, chills/rigors, and nausea/vomiting) occur during an infusion, the infusion should be slowed or interrupted and supportive treatment should be instituted at the discretion of the Investigator. After resolution of symptoms, if the infusion had been slowed, the original infusion rate may be resumed; if the infusion had been interrupted, the infusion may be restarted at a rate that does not exceed the original infusion rate. An infusion must be discontinued if not completed within 3 hours.

Refer to the Directions for Handling and Administration (DHA) for infusion rate information.

If a severe infusion-related reaction occurs during an infusion, or an allergic reaction such as urticaria or anaphylaxis occurs, the subject will be discontinued from study treatment but may remain in the study. The subject must be appropriately treated in accordance with local practice.

Severity of events is described in Section 15.2.3.

7.3. Overall Study Duration and Follow-Up

The study period will consist of Screening, treatment, and FU.

The double-blind, placebo-controlled period of the study will consist of an 8-week screening period, a 76-week treatment period, and a safety FU period of 18 weeks after the final dose.

Subjects will have approximately 32 scheduled clinic visits during the placebo-controlled period, and up to 8 telephone safety FU contacts, as follows:

- Screening Visits no more than 60 days before the first dose of study treatment on Day 1 (visits will be conducted on multiple days). It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.
- 20 outpatient dosing visits.
- 8 telephone safety FU contacts approximately 2 weeks after each of the first 8 doses.
- 3 visits for clinical assessments.
- 2 visits (including baseline) for CSF biomarkers (optional). Note: CSF collection at Screening using study-specific procedures is preferred; however, if a CSF sample has been obtained within 3 months prior to Screening, this sample may be used in lieu of requiring that the subject undergo a lumbar puncture (LP) at Screening.
- 3 visits (including Screening) for amyloid PET scan (in a subset of subjects).
- 2 visits (including baseline) for tau PET scan (in a subset of subjects, where available).
- 7 visits for brain MRI.

- 1 FU safety visit at Week 94 (only for subjects not entering the LTE period) or 18 weeks after last administration of study treatment for those subjects who withdraw from study.

Subjects who meet the LTE inclusion and exclusion criteria will be eligible to enter the LTE period. Subjects who enter the LTE period will have approximately up to 76 additional planned clinic visits, and up to 8 telephone safety FU contacts, as follows:

- 65 outpatient dosing visits.
- 8 telephone safety FU contacts approximately 2 weeks after each of the first 8 doses.
- 7 visits for clinical assessments.
- 2 visits for CSF biomarkers (optional).
- 4 visits for amyloid PET scan (in a subset of subjects).
- 2 visits for tau PET scan (in a subset of subjects, where available).
- 10 visits for brain MRI.
- 1 FU safety visit.

Subjects who have a change in AD medication (other than study treatment) during the placebo-controlled or LTE period should have an unscheduled visit; all clinical assessments for the primary and secondary endpoints should be performed prior to the change in medication.

Subjects who experience ARIA during the placebo-controlled or LTE period should have unscheduled visits per the guidelines in Section 7.2.1.

7.3.1. Screening

During the Screening Visit, under a separate (optional) initial consent process, subjects can complete the neurocognitive scales (CDR, MMSE, the Repeatable Battery for Assessment of Neuropsychological Status [RBANS]) and ApoE genotyping. This initial neurocognitive screening is intended to reduce the burden on subjects and sites by avoiding unnecessary testing if subjects do not meet key inclusion criteria. If the subject meets inclusion criteria for these 3 scales, then the full consent process must be completed prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process, which would allow the administration of all screening assessments.

The neurocognitive assessments that have exclusion cut points (CDR, MMSE, and RBANS) and ApoE genotyping must be performed at Screening Visit 1. ApoE genotyping may be performed at Visit 1 prior to other screening assessments. The ADAS-Cog 13 and ADCS-ADL-MCI will be performed at Screening Visit 2 within 20 days after Visit 1 and must NOT be performed on the same day as the CDR, MMSE, and RBANS. The NPI-10 can be performed at any time during Screening as long as it is performed after the CDR (e.g., including at Screening Visit 1). All other cognitive assessments as well as CSF collection may be performed at any time during Screening after eligibility is confirmed during Screening Visit 1. CSF collection at Screening using study-specific procedures is preferred; however, if a CSF sample has been obtained within

3 months prior to Screening, this sample may be used in lieu of requiring an LP at Screening. The MRI at Screening Visit 2 should be done only after the subject eligibility based on clinical and laboratory criteria is confirmed during Screening Visit 1. The PET scan at Screening Visit 3 should be completed only after the MRI inclusion criterion is met.

Subject eligibility for the study will be determined no more than 60 days prior to study entry. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.

Subjects who fail Screening will be permitted to be rescreened once at the Sponsor's discretion. Subjects who fail Screening due to not meeting entry criteria for PET, MMSE, hepatitis B or C results, having a CDR global score >0.5, or having abnormal MRI findings will not be allowed to rescreen. Note: Subjects with a CDR global score of 0 but who meet the other entry criteria may repeat the screening CDR evaluation after 6 months of the initial evaluation.

Subjects who fail Screening because allowed chronic medications have not been at stable doses for at least 4 weeks prior to Screening Visit 1 or whose use of AD medications has not been at stable doses for at least 8 weeks prior to Screening Visit 1 may return for rescreening after use of these medications has been stabilized for the required period.

7.3.2. Treatment

Eligible subjects will report to the study site to receive study treatment every 4 weeks for 76 weeks (20 doses). All subjects who meet the LTE inclusion and exclusion criteria will be eligible to enter the LTE period and will receive study treatment every 4 weeks for up to an additional 256 weeks (65 doses), with the first dose administered approximately 4 weeks after the final dose in the placebo-controlled period of the study. Subjects will continue treatment once every 4 weeks, until Week 336, or until the last subject has had his or her Week 182 Visit, whichever occurs first.

7.3.3. Follow-Up

All subjects participating in the placebo-controlled period are to return to the study site approximately 2 weeks after the final dose for clinical assessments.

Subjects participating in the placebo-controlled period and not entering the LTE period are to return to the study site for a FU Visit at Week 94 (18 weeks after the last placebo-controlled period dose). The final study visit for these subjects will be Week 94.

Subjects who participate in the LTE period are to return to the study site to receive their first LTE dose approximately 4 weeks after their last dose in the placebo-controlled period of the study. A FU Visit will occur 18 weeks after the last LTE period dose. The timing of the final study visit for subjects participating in the LTE period will vary, since the EOT Visit for a subject who participates in the LTE period will occur at Week 338, or when the last subject has had his or her Week 182 Visit, whichever occurs first.

Subjects who discontinue treatment are to remain in the study, attend a FU Visit 18 weeks after the final dose, and immediately continue protocol-required tests and assessments at a subset of

the clinic visits (see Table 10 and Table 11) until the end of the study or until withdrawal of consent. Subjects who withdraw from the study are encouraged to return for FU assessments 18 weeks after their last dose of study treatment.

7.4. Study Stopping Rules

Biogen may terminate this study at any time, after informing Investigators. Biogen (or designee) will notify Investigators when the study is to be placed on hold, completed, or terminated.

Dosing may be terminated by the Sponsor at the recommendation of the IDMC, based exclusively on safety and tolerability data or following the futility analysis, or at the discretion of the Sponsor; therefore, there are no study-specific stopping rules defined in this protocol.

7.5. End of Study

The end of study is last subject, last visit. The EOT Visit for a subject who continues in the study will occur at Week 338, or when the last subject has had his or her Week 182 Visit, whichever occurs first.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at Screening or at the timepoint specified in the individual eligibility criterion listed:

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.
2. Aged 50 to 85 years old, inclusive, at the time of informed consent.
3. All women of childbearing potential and all men must practice highly effective contraception during the study and for 24 weeks after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 15.5.
4. Must have at least 6 years of education or work experience to exclude mental deficits other than MCI or mild AD.
5. Must have a positive amyloid PET scan. Previously obtained PET scan (within 12 months of Screening) is permissible for subjects not participating in the amyloid PET substudy. Previous PET scan images must be submitted to the central imaging vendor to confirm study inclusion criteria are met.
6. Must meet all of the following clinical criteria for MCI due to AD or mild AD according to NIA-AA criteria [Albert 2011; McKhann 2011], and must have:
   - A CDR global score of 0.5.
   - An RBANS score of 85 or lower indicative of objective cognitive impairment (based upon the Delayed Memory Index score).
   - An MMSE score between 24 and 30 (inclusive).
7. Apart from a clinical diagnosis of early AD, the subject must be in good health as determined by the Investigator, based on medical history and screening assessments.
8. Must consent to ApoE genotyping.
9. Has one informant/care partner who, in the Investigator's opinion, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally be available by phone to provide information to the Investigator and study staff about the subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study, and the use of the same informant/care partner for the duration of the study is encouraged.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening, or at the timepoint specified in the individual criterion listed:

Medical History

1. Any uncontrolled medical or neurological/neurodegenerative condition (other than AD) that, in the opinion of the Investigator, might be a contributing cause of the subject's cognitive impairment (e.g., substance abuse, vitamin B_{12} deficiency, abnormal thyroid function, stroke or other cerebrovascular condition, Lewy body dementia, fronto-temporal dementia, head trauma).
2. Clinically significant unstable psychiatric illness (e.g., uncontrolled major depression, uncontrolled schizophrenia, uncontrolled bipolar affective disorder) within 6 months prior to Screening.
3. Transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year prior to Screening.
4. Brain MRI performed at Screening (per centrally read MRI) that shows evidence of any of the following:
   - Acute or sub-acute hemorrhage.
   - Prior macrohemorrhage (defined as >1 cm in diameter on T2* sequence) or prior subarachnoid hemorrhage unless it can be documented that the finding is not due to an underlying structural or vascular abnormality (i.e., finding does not suggest subject is at risk of recurrent hemorrhage).
   - Greater than 4 microhemorrhages (defined as ≤1 cm in diameter on T2* sequence).
   - Cortical infarct (defined as >1.5 cm in diameter; irrespective of anatomic location).
   - >1 lacunar infarct (defined as ≤1.5 cm in diameter).
   - Superficial siderosis.
   - History of diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scale [Wahlund 2001].
   - Any finding that, in the opinion of the Investigator, might be a contributing cause of subject's dementia, might pose a risk to the subject, or might prevent a satisfactory MRI assessment for safety monitoring.
5. History of bleeding disorder or predisposing conditions, blood clotting or clinically significant abnormal results on coagulation profile at Screening, as determined by the Investigator.
6. Presence of diabetes mellitus that, in the judgment of the Investigator, cannot be controlled or adequately managed.

7. History of unstable angina, myocardial infarction, chronic heart failure (New York Heart Association Class III or IV), or clinically significant conduction abnormalities (e.g., unstable atrial fibrillation) within 1 year prior to Screening.
8. Clinically significant 12-lead ECG abnormalities, as determined by the Investigator.
9. Uncontrolled hypertension defined as: average of 3 systolic blood pressure [SBP]/diastolic blood pressure [DBP] readings >165 mmHg and/or >100 mmHg at Screening (blood pressure measurements exceeding these limits may be repeated as warranted by the Investigator, but values must be within the specified limits for the subject to be eligible for the study), or persistent SBP/DBP readings >180 mmHg and/or >100 mmHg 3 months prior to randomization (Day 1) that, in the opinion of the Investigator, are indicative of chronic uncontrolled hypertension.
10. History of malignancy or carcinoma. The following exceptions may be made after discussion with the Sponsor:
    - Subjects with cancers in remission more than 5 years prior to Screening.
    - Subjects with a history of excised or treated basal cell or squamous carcinoma of the skin.
    - Subjects with localized prostate cancer with treatment cycles that completed at least 6 months prior to Screening.
11. History of seizure within 10 years prior to Screening.
12. Indication of impaired liver function as shown by an abnormal liver function profile at Screening (e.g., repeated values of aspartate aminotransferase [AST] and alanine aminotransferase [ALT] $\geq 2 \times$ the upper limit of normal).
13. History or evidence of an autoimmune disorder considered clinically significant by the Investigator or requiring chronic use of systemic corticosteroids or other immunosuppressants.
14. Recent history (within 1 year of Screening) of alcohol or substance abuse as determined by the Investigator, a positive urine drug (due to non-prescription drug) or alcohol test at Screening, or use of cannabinoids (prescription or recreational).
15. Clinically significant systemic illness or serious infection (e.g., pneumonia, septicemia) within 30 days prior to or during Screening.
16. History of or known seropositivity for human immunodeficiency virus (HIV).
17. History of or positive test result at Screening for hepatitis C virus antibody or hepatitis B virus (defined as positive for both hepatitis B surface antigen AND hepatitis B core antibody).
18. History of severe allergic or anaphylactic reactions, or history of hypersensitivity to any of the inactive ingredients in the drug product (refer to the IB for information on the clinical formulation).

19. Any other medical conditions (e.g., renal disease) that are not stable or controlled, or, which in the opinion of the Investigator, could affect the subject's safety or interfere with the study assessments.

Medications

20. Any medications that, in the opinion of the Investigator, may contribute to cognitive impairment, put the subject at higher risk for AEs, or impair the subject's ability to perform cognitive testing or complete study procedures.
21. Use of allowed chronic medications at doses that have not been stable for at least 4 weeks prior to Screening Visit 1 and during Screening up to Study Day 1, or use of AD medications (including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine) at doses that have not been stable for at least 8 weeks prior to Screening Visit 1 and during Screening up to Study Day 1.
22. Use of medications with platelet anti-aggregant or anti-coagulant properties (the use of aspirin at a prophylactic dose [≤ 325 mg daily] is allowed).
23. Use of illicit narcotic medication.
24. Vaccinations within 10 days prior to randomization (Day 1).
25. Participation in any active immunotherapy study targeting Aβ unless documentation of receipt of placebo is available.
26. Participation in any passive immunotherapy study targeting Aβ within 12 months of Screening unless documentation of receipt of placebo is available.
27. Participation in any study with purported disease-modifying effect in AD within 12 months prior to Screening unless documentation of receipt of placebo is available. Subjects who developed ARIA-E during a previous disease-modifying trial should be excluded.
28. Participation in a previous study with aducanumab (subject is eligible if he/she did not receive active aducanumab).

Study Procedures

29. Contraindications to having a brain MRI (e.g., pacemaker; MRI-incompatible aneurysm clips, artificial heart valves, or other metal foreign body; claustrophobia that cannot be medically managed).
30. Contraindication to having a PET scan (e.g., inability to lie flat or still for the duration of the scan) or intolerance to previous PET scans (i.e., previous hypersensitivity reactions to any PET ligand or imaging agent, failure to participate in and comply with previous PET scans).
31. A negative PET scan result with any amyloid-targeting ligand within 6 months prior to Screening.
32. Have had or plan exposure to experimental radiation within 12 months prior to Screening such that radiodosimetry limits would be exceeded by participating in this study.

33. For subjects who consent to LP, any contraindications to having a LP (e.g., platelet count <100,000/μL, lumbar spine deformity). Any symptoms caused by or related to the optional LP during Screening must be resolved prior to randomization (Day 1). Subjects may still participate in the overall study even if participation in the optional LP portion is contraindicated.

Others

34. Female subjects who are pregnant or currently breastfeeding.
35. Previous participation in this study. Subjects who fail Screening will be permitted to be rescreened once at the Sponsor's discretion, except those who fail due to PET, MMSE, CDR global score >0.5, hepatitis B or C, or abnormal MRI findings. (Subjects who fail Screening due to a CDR global score of 0 may be rescreened; such subjects will be allowed to repeat the screening CDR assessment after 6 months.)
36. Subject currently living in an organized care facility with extensive intervention and/or support of daily living activities.
37. Blood donation (≥ 1 unit) within 1 month prior to Screening.
38. Inability to comply with study requirements.
39. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

8.3. Inclusion Criteria for Long-Term Extension Period

To be eligible to participate in the LTE period, subjects must meet the following eligibility criteria at Week 78:

1. Subject must have completed the placebo-controlled period of the study including the Week 78 Visit. Subject must have taken at least 14 doses and not have missed more than 4 consecutive doses, except for subjects whose dose was suspended due to ARIA (See Section 7.2.1). Subjects who do not meet these criteria may enter the LTE period only with Sponsor's approval.
2. The subject (or the subject's legally authorized representative) has the ability to understand the purpose and risks of the study and provide signed and dated informed consent (or assent) and authorization to use confidential health information in accordance with national and local subject privacy regulations.
3. Female subjects of childbearing potential and male subjects must practice highly effective contraception during the study and for 24 weeks after their last dose of study treatment.
4. Apart from a clinical diagnosis of AD, the subject must be in good health as determined by the Investigator, based on medical history.
5. Must have the ability to comply with procedures for protocol-related tests.

6. Has one informant/care partner who, in the Investigator's opinion, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally be available by phone to provide information to the Investigator and study staff about the subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study, and the use of the same informant/care partner for the duration of the study is encouraged.

8.4. Exclusion Criteria for Long-Term Extension Period

Subjects will be excluded from entering the LTE period if at Week 78 they have:

1. Any medical or psychiatric contraindication or clinically significant abnormality that, in the opinion of the Investigator, will substantially increase the risk associated with the subject's participation in and completion of the study.

9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

9.1. Screening and Enrollment

Subjects (or their legally authorized representative, where applicable) must provide informed consent before any screening tests are performed (see Section 17.3). During Screening, subjects can complete the neurocognitive scales (CDR, MMSE and RBANS) and ApoE genotyping to determine study eligibility under a separate, optional initial consent process. If the subject meets inclusion criteria for these 3 scales the full consent process must be completed prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process which would allow the administration of all screening assessments. When a subject signs the full informed consent form (ICF), that subject is considered to be enrolled in the study. ApoE genotyping may be performed at Visit 1 prior to other screening assessments.

Participating study sites are required to document all screened candidates initially considered for inclusion in this study. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log. The total study duration for each subject participating only in the placebo-controlled period will be approximately 102 weeks (approximately an 8-week screening period, 76 weeks of placebo or aducanumab dosing, and 18 weeks of FU).

9.2. Randomization and Registration of Subjects

Subjects will be registered at the Screening Visit and randomized only after all baseline assessments have been completed and the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. No subject may begin treatment prior to assignment of a unique identification number (registration) and randomization. Any subject identification numbers or randomization schedule assignments that are assigned will not be reused even if the subject does not receive treatment. Rescreened subjects will be assigned a new number.

Subjects will be randomized to receive aducanumab low dose:aducanumab high dose:placebo in a 1:1:1 ratio. The randomization will be stratified by site and ApoE ε4 status (carrier or non-carrier). Subjects randomized to placebo at the start of the placebo-controlled period will also be randomized to receive dose-blinded aducanumab (low dose:high dose, 1:1 ratio) for the LTE period and randomization will be stratified by subject ApoE ε4 carrier status. Treatment group assignments for the placebo-controlled period and the LTE period will be assigned at Study Day 1. Enrollment will be monitored, via the IRT, such that the population of subjects with mild AD represents a small percentage of the total enrolled in the trial. Subjects who withdraw from the study may not be replaced.

Refer to the Study Reference Guide for details on registration and randomization.

9.3. Blinding Procedures

This study consists of a randomized, double-blind, placebo-controlled period, followed by a dose-blinded LTE period with all subjects receiving aducanumab.

For the double-blinded placebo-controlled period, all study staff who conduct subject assessments will be blinded to the subject treatment assignments. The rating HCPs should remain blinded to treatment assignment as well as subject care management and only have access to the information necessary to carry out their responsibilities as detailed in Section 4.3.1. As a placebo match is not provided for the study, unblinded pharmacy staff are required to manage all aspects of study treatment receipt, dispensing, and preparation. To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Biogen or its representatives, except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded IQVIA or Biogen safety staff.

For the LTE period, the dose information must remain restricted. The rating and treating HCP should remain blinded to treatment assignment and only have access to the information necessary to carry out their responsibilities as detailed in Section 4.3.1. To maintain the study blind, it is imperative that dose information is not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Biogen or its representatives, except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded IQVIA or Biogen safety staff.

10. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

A subject *must* permanently discontinue study treatment for any of the following reasons:

- The subject develops any of the following:
  - ARIA-E accompanied by serious clinical symptoms except for "other medically important event" as defined in Table 13.
  - Symptomatic ARIA-H (microhemorrhages) with serious clinical symptoms except for "other medically important event" as defined in Table 14.
  - Symptomatic ARIA-H (superficial siderosis) with or serious clinical symptoms except for "other medically important event" as defined in Table 15.
  - ARIA-H with ≥ 10 microhemorrhages and/or >2 focal areas of superficial siderosis.
  - Any new incident macrohemorrhage (defined as >1 cm in diameter on T2* sequence).

  See Section 7.2.1 for full details regarding discontinuation and dose reduction due to ARIA-E or ARIA-H.
- The subject becomes pregnant. Study treatment must be discontinued immediately and pregnancy must be reported according to the instructions in Section 15.4.1.
- The subject withdraws consent to continue study treatment.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment or unblinding of the subject's treatment assignment.
- The subject experiences an AE that does not resolve or requires continued treatment that meets exclusionary criteria (see Section 11.5.1.2).
- The subject experiences a severe infusion reaction.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Investigator or Sponsor for noncompliance.

The reason for discontinuation of study treatment must be recorded in the subject's case report form (CRF).

A subject who discontinues treatment is to remain in the study, attend a FU Visit 18 weeks after the final dose, and immediately continue protocol-required tests and assessments at a subset of the clinic visits (see Table 10 and Table 11) until the end of the study per the schedule of events or until the subject withdraws consent.

10.2. Withdrawal of Subjects From Study

Subjects must be withdrawn from the study for any one of the following reasons:

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator or Sponsor.

Note: A subject who discontinues study treatment will not be automatically withdrawn from the study, regardless of the number of doses missed. The subject is to remain in the study, and continue with a FU Visit 18 weeks after the final dose, and protocol-required tests and assessments at a subset of the clinic visits (see Table 10 and Table 11) until the end of the study or until the subject withdraws consent.

The reason for the subject's withdrawal from the study must be recorded in the subject's CRF.

Subjects who are withdrawn from the study after receiving ≥ 1 doses of study treatment should complete the EOT Visit after the reason for withdrawal is identified. For such subjects, efficacy assessments specified at the EOT Visit are not required if the subject discontinues treatment within 3 months of the previous efficacy assessment visit and no significant changes in cognitive status are suspected by the Investigator; The site should notify the sponsor in such cases. Subjects who are withdrawn from the study are also to return to the site for a FU Visit 18 weeks after receiving their last dose of study treatment.

11. STUDY TREATMENT USE

11.1. Regimen

Refer to and follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

Please see Section 4.2 (Schedule of Events) for the study treatment infusion schedule during the placebo-controlled and LTE periods of the study.

Aducanumab is to be administered by IV infusion following dilution into saline. See Section 12 for details of aducanumab study treatment.

11.1.1. Aducanumab

The Sponsor will provide aducanumab to study sites.

11.1.2. Placebo

Placebo (CCI sodium chloride) will be supplied by the study site.

11.2. Modification of Dose and/or Treatment Schedule

Refer to Section 7.2.1 (dose suspension) and Section 7.2.2 (infusion interruption). Doses should be administered at least 21 days apart. If the dosing interval cannot be met, the dose administration should be assessed by the study medical monitor.

11.3. Precautions

Not applicable.

11.4. Compliance

Compliance with treatment dosing is to be monitored and recorded by unblinded site staff.

11.5. Prior and Concomitant Therapy and Procedures

11.5.1. Prior and Concomitant Therapy

Prior AD medication use within the 12 months prior to Screening will be captured.

A concomitant therapy is any drug or substance administered between the informed consent and until the subject's final clinic visit (including the FU Visit).

No premedication (e.g., anti-allergy drugs, antipyretic analgesics) should be used prior to the start of study treatment infusion unless discussed with the study medical monitor in advance.

11.5.1.1. Allowed Concomitant Therapy

- Medications for chronic conditions are allowed at a stable dose during the study as long as the subject has been stable on the medication(s) for at least 4 weeks prior to Screening Visit 1 and during the screening period.
- Symptomatic therapies for AD, including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine, are allowed provided that subjects are receiving a stable dose for at least 8 weeks prior to Screening Visit 1 and during the screening period and that they stay on a stable dose while in the study.
- Vaccinations with live or attenuated vaccines are allowed during the study. Administration of any vaccination/booster should not be given < 10 days prior to any dosing visit and for 10 days after a dosing visit.

11.5.1.2. Disallowed Concomitant Therapy

- Medications with platelet anti-aggregant or anti-coagulant properties, except the use of aspirin at a dose of ≤ 325 mg per day.
- Non-prescription narcotic medication.
- Immunosuppressive drugs (including systemic corticosteroids). Local corticosteroids (including inhaled and topical corticosteroids) are allowed; certain systemic corticosteroids may be permitted at the Sponsor's discretion.
- Parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange, and plasmapheresis.
- Any investigational drug.

Subjects should be instructed to continue the medications that they were receiving at enrollment without any changes (see allowed concomitant therapy above) and avoid starting any new medications or herbal preparations during the study period, as it may confound the results of the study. However, medically indicated medication or treatment should not be withheld. Subjects should inform the Investigator of any changes in medication. The change should be reviewed by the Investigator and the study medical monitor to determine whether the subject's study treatment should be suspended. Medications used to treat AEs would not result in automatic permanent study treatment discontinuation. However, as noted in Section 10.1, if a subject requires continued use of a disallowed therapy, the subject must permanently discontinue study treatment. The Sponsor may be consulted if required.

Subjects should have an unscheduled visit for a change in AD medication, and all clinical assessments for the primary and secondary objectives should be performed prior to the change in medication.

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, routine colonoscopy, bacterial cultures)

performed between the time the subject is enrolled in the study and until the subject's final clinic visit (including FU Visit), unless the subjects is being followed for study-related toxicity.

The use of concomitant therapies or procedures defined above must be recorded on the subject's CRF. AEs related to administration of these therapies or procedures must be documented on the appropriate AE CRF.

11.6. Continuation of Treatment

No further provisions are made for access to the study treatment. If aducanumab is proven to be beneficial, all regulatory requirements regarding poststudy access will be met.

12. STUDY TREATMENT MANAGEMENT

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Study treatment vials are for one-time use only; any study treatment remaining in the vial must not be used for another subject.

12.1. Aducanumab

Research Name: BIIB037

Generic Name: Aducanumab

Trade Name(s): Not applicable

Synonyms: Fully human, IgG_1, anti-Aβ monoclonal antibody

Aducanumab is a recombinant human antibody expressed in a Chinese hamster ovary cell line, purified to a high degree of purity and formulated as a liquid. Aducanumab is an IgG_1 consisting of 2 heavy and 2 kappa light chains connected by inter-chain disulfide bonds. Aducanumab has 1 carbohydrate moiety linked to Asn-304. Aducanumab is purified from the media and formulated as a liquid.

Aducanumab is supplied as a liquid drug product containing either:

- aducanumab CCI (excipients: sodium citrate, citric acid, L-arginine hydrochloride, and polysorbate-80)

  or

- aducanumab CCI excipients: L-histidine hydrochloride, L-histidine free base, L-arginine hydrochloride, L-methionine, and polysorbate-80)

The concentration for each vial (either CCI appears on the label. Aducanumab is manufactured in accordance with Good Manufacturing Practices.

The contents of the label will be in accordance with all applicable regulatory requirements. Aducanumab should not be used after the expiration date.

12.1.1. Aducanumab Preparation

The individual preparing aducanumab should carefully review the instructions provided in the DHA.

Aducanumab is to be administered by IV infusion following dilution into saline.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the vials or drug it should not be used. The vial in question should be saved at the study site, and the problem immediately reported to Biogen.

12.1.2. Aducanumab Storage

Study treatment must be stored in a secure location. Aducanumab is to be stored at 2°C to 8°C (36°F to 46°F), in a locked storage container with limited access. Aducanumab should be protected from light, protected from freezing, and should not be shaken. If administration of the prepared aducanumab is delayed for more than 4 hours, then it should be kept at 2°C to 8ºC until use. If administration of the prepared aducanumab is delayed for more than 24 hours, it must be discarded. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

12.1.3. Aducanumab Handling and Disposal

The Investigator must return all used and unused vials of aducanumab as instructed by Biogen (or its designee), unless approved for onsite destruction.

If any aducanumab supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from Biogen by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Biogen must be notified in writing of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. Aducanumab Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), and accounts of any study treatment accidentally or deliberately destroyed.

Unless otherwise notified, all vials both used and unused, must be saved for study treatment accountability. By the end of the study reconciliation must be made between the amount of aducanumab supplied, dispensed, and subsequently destroyed or returned to Biogen. A written explanation must be provided for any discrepancies.

12.2. Placebo

The placebo CCI sterile sodium chloride for injection) will be provided by the site in the form of 100 mL saline IV bags.

12.3. Additional Protocol-Designated Products

Refer to the DHA for infusion-related supply specifications.

To confirm amyloid pathology at Screening, PET scans will be performed using Amyvid™ (^{18}F-florbetapir), Vizamyl™ (^{18}F-flutemetomol), or Neuraceq™ (^{18}F-florbetaben). For those subjects participating in the amyloid PET substudy, Screening and FU scans must be performed

using Amyvid and for subjects participating in the PET substudy in Japan, Vizamyl (^{18}F-flutemetomol) may also be used. For details on PET imaging ligands, including tau PET, refer to the procedural manual for PET.

13. EFFICACY, PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS

Refer to Section 4.2 for the timing of assessments.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of aducanumab:

- CDR
- MMSE
- ADAS-Cog 13
- ADCS-ADL-MCI
- NPI-10

It is recommended that clinical assessments be performed at the same time of day for subjects during their study visits.

Some tests will require the informant/care partner to participate and answer questions regarding the subject's daily activities and cognitive capabilities.

The recommended order of administration of the clinical assessments is described in the Study Reference Guide.

13.2. Pharmacokinetic Assessments

Serum concentrations of aducanumab will be measured using a validated assay.

13.3. Pharmacodynamic Assessments

The following tests will be performed to assess the PD properties of aducanumab:

- Serial measurement of amyloid plaque burden in certain areas of the brain as measured by amyloid PET (in a subset of approximately 400 subjects participating in the amyloid PET cohort).

  Only sites with capabilities of performing ^{18}F-florbetapir PET will be allowed to perform this assessment. Investigator participation in this part of the study is optional and contingent upon approval by his/her ethics committee (EC) or institutional review board (IRB). If the Investigator is not participating or the test is not approved by his/her EC/IRB, the relevant section of the ICF will not be applicable to that site.

  Subject participation in this part of the study is optional at participating sites. Informed consent must be recorded in the CRF. Detailed PET scanning protocols will be described in a separate procedural manual for PET. Approximately 400 subjects are expected to participate in the amyloid PET substudy.

- Whole brain volume, hippocampal volume, ventricle volume, and cortical gray matter volume measured by MRI.

  Detailed MRI scanning protocols will be described in the procedural manual for MRI.

- Functional connectivity as measured by tf-fMRI (in a subset of sites and subjects, where available).

  Only sites with capabilities of performing tf-fMRI will be allowed to perform this assessment. Detailed tf-fMRI scanning protocols will be described in the procedural manual for MRI.

- Cerebral blood flow as measured by ASL-MRI (in a subset of sites and subjects, where available).

  Only sites with capabilities of performing ASL-MRI will be allowed to perform this assessment. Detailed ASL-MRI scanning protocols will be described in the procedural manual for MRI.

- Disease- or treatment-related blood and CSF biomarkers. Subject participation in CSF collection is optional (see Section 13.4.1).

- Tau PET signal (in a subset of sites and subjects, where available).

13.4. Additional Assessments

13.4.1. CSF Biomarkers (Lumbar Puncture Test)

An optional CSF collection will be conducted at sites. Investigator participation in this part of the study is optional and contingent upon approval by the site's EC/IRB. If the Investigator is not participating or the test is not approved by the site's EC/IRB, the relevant section of the ICF will not be applicable to that site.

Subject participation in the LP test is optional at participating sites. Informed consent must be recorded in the CRF.

Analyses of CSF samples will include, but are not limited to, the following:

- Disease- or treatment-related biomarker levels (e.g., amyloid and tau proteins).
- Cell count and differential (to be conducted by the local laboratory).
- Total protein (to be conducted by the central laboratory).

Four LPs are to be performed (1 at Screening, 1 in the placebo-controlled period, and 2 in the LTE period). CSF collection at Screening using study-specific procedures is preferred; however, if a CSF sample has been obtained within 3 months prior to Screening, this sample may be used in lieu of requiring an LP at Screening. Any symptoms caused by or related to the LP must be resolved or stabilized, in the opinion of the Investigator, prior to infusion. Vital signs will be obtained before the LP at each visit for subjects participating. Guidance on LPs will be provided in the Study Reference Guide.

13.4.2. ApoE Genotyping

Whole blood samples for deoxyribonucleic acid (DNA) ApoE genotyping will be collected from all subjects at the Screening Visit.

13.4.3. Optional DNA Test

Where local regulations and ethics committee approval allow, an optional DNA sample will be collected for future genetic analysis. This optional 1-time blood collection requires additional consent from the subject.

Genetic polymorphism in genes encoding drug targets or the downstream pathways, as well as proteins that impact drug absorption, distribution, metabolism, and elimination, may affect the safety and efficacy of aducanumab.

In the event of an unusual response or observation of unexplained AEs, DNA samples may be used to determine if there are any pharmacogenetic associations with drug response.

In the future, as the understanding of AD, disease-modifying AD treatments and/or aducanumab, additional genetic analyses may be warranted to refine the knowledge of the molecular basis of the disease and the drug response and to advance the development of novel therapeutics. The samples may also be used to understand the biology of other diseases and traits of interest to Biogen.

The DNA samples will be coded with the subject's identification number and stored for 15 years or a duration dictated by local, national, or regional laws or regulations. No genotyping or genetic data will be provided to the subject. Subjects may withdraw consent and request to have their sample destroyed at any time and no further genetic data will be generated; any data already generated will not be destroyed.

13.4.4. Health Outcomes Assessments

The following assessments will be performed to evaluate the effect of aducanumab in subjects and caregivers:

- EQ-5D (SR)
- EQ-5D (IR-S)
- EQ-5D (IR-I)
- mPDQ-20
- CAM

Some tests will require the informant/care partner to participate and answer questions regarding the subject's daily activities and cognitive capabilities.

The recommended order of administration of the clinical assessments is described in the Study Reference Guide.

13.5. Future Scientific Research Assessments

In subjects who provide additional optional consent, serum, plasma, CSF and ribonucleic acid samples may be collected and residual samples may be stored for future, unspecified, exploratory biomarker analysis. Subjects will sign a separate, written ICF if they agree to this sample collection and/or to their samples being used in this way.

The samples collected may be utilized to identify or verify putative, prognostic, and predictive markers associated with disease and markers of therapeutic response to treatment, and/or to develop diagnostic and analytical tests. Background and dynamic clinical disease characteristics and associated biomarker data may be utilized to predict subsequent disease worsening (severity), identify high-risk patient subgroups, and identify predictors of response to treatment.

14. SAFETY ASSESSMENTS

See Section 4.2 for the timing of assessments.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of aducanumab:

- AE and SAE monitoring.
- Physical examination, including height and weight.
- Neurological examination.
- Vital signs (body temperature, heart rate, SBP, DBP, and respiratory rate).
- 12-lead ECG.
- Brain MRI.
- Concomitant medication, therapy, and procedure monitoring.
- MOCA (for ARIA monitoring and management).
- Columbia Suicide Severity Rating Scale (C-SSRS).

14.2. Laboratory Safety Assessments

The following laboratory assessments will be performed to evaluate the safety profile of aducanumab

- Hematology: complete blood count with differential and platelet count, and absolute neutrophil count.
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, ALT, AST, lactate dehydrogenase, gamma-glutamyl-transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, and potassium.
- Urinalysis: color, specific gravity, pH, protein, glucose, blood, ketones, and microscopic examination (if abnormal).
- Serum and urine pregnancy test for women of childbearing potential only.
- Coagulation, virology (including HIV at the Investigator's discretion after consideration of risk factors), HbA_{1c}, and alcohol/drug screen at Screening.

14.3. Immunogenicity Assessments

Presence of serum anti-aducanumab will be determined using a validated assay. A standard 3-tier antidrug antibody (ADA) approach will be used (i.e., screening assay, confirmatory assay, and titration assay). Additional characterization of the immune response may be performed.

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject or his/her legally authorized representative must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Determination of whether an abnormal laboratory value meets the definition of an AE will be made by the Investigator. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE.
- A laboratory test result that requires the subject to receive specific corrective therapy.
- A laboratory abnormality that the Investigator considers to be clinically significant.

Pre-treatment, nonserious AEs that occur within 48 hours after receipt of a ligand will be captured by the sites on the AE form.

15.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

15.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject is hospitalized. The study site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
  - If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 15.1.2 is met.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2.
- The relationship of the event to study treatment as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment.

Relationship of Event to Study Treatment	
Not related	An AE will be considered "not related" to the use of the investigational drug if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include but are not limited to: the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of the investigational drug if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of an alternative explanation for the AE.

15.2.3. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by Biogen according to the IB for aducanumab.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and the subject's final clinic visit (including FU Visit) is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment. Pre-treatment, nonserious AEs that occur within 48 hours after receipt of a ligand will be captured by the sites on the AE form.

15.3.2. Adverse Events of Special Interest

ARIA-E and ARIA-H are considered AEs of special interest and will be entered on the Adverse Event of Special Interest CRF within 72 hours following the receipt of abnormal MRI findings from the central MRI reader.

AE reporting for ARIA-E and ARIA-H will be based on the following centrally read MRI sequences: fluid attenuated inversion recovery/T2 for ARIA-E and T2*/gradient echo for ARIA-H.

If the event qualifies as an SAE an SAE form should be submitted per the guidelines in Section 15.3.4. Investigators should include a copy of the centrally read MRI report when submitting the SAE form to IQVIA Lifecycle Safety.

15.3.3. Serious Adverse Events

Any SAE experienced by the subject between signing of the ICF and the subject's final clinic visit (including FU Visit) will be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to Biogen (or designee) within 24 hours as described in Section 15.3.4. This also applies to SAEs that occur after administration of the ligand. FU information regarding an SAE also must be reported with 24 hours.

Events occurring after the subject's final clinic visit (including FU Visit) should be reported to Biogen only if the Investigator considers the SAE related to study treatment.

Any SAE that is ongoing when the subject completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

15.3.4. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify IQVIA Lifecycle Safety within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any SAE that occurs between the time that the subject has signed the ICF and the subject's final clinic visit (including FU Visit) must be reported to IQVIA Lifecycle Safety within 24 hours of the study site staff becoming aware of the event. Thereafter, the event should be reported only if the Investigator considers it related to study treatment.

A report ***must be submitted*** to IQVIA Lifecycle Safety regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject has received study treatment
- The severity of the event

- The relationship of the event to study treatment

To report initial or FU information on an SAE, fax or email a completed SAE form. Refer to the Study Reference Guide for country-specific IQVIA Lifecycle Safety fax numbers or email PPD

15.3.4.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to IQVIA Lifecycle Safety. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.5. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen to be related to the study treatment administered.

Appropriate personnel in Biogen Safety and Benefit Risk (SABR) will unblind SUSARs for the purpose of regulatory reporting. Biogen or designee will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Biogen or designee will submit SUSARs to Investigators in a blinded fashion.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

Subjects should not become pregnant or impregnate their partners during the study and for 24 weeks after their last dose of study treatment. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy occurring in a female subject by faxing the appropriate form to IQVIA Lifecycle Safety within 24 hours of the study site staff becoming aware of the pregnancy at the SAE reporting fax number provided in the study reference manual. The Investigator or study site staff must report the outcome of the pregnancy to IQVIA Lifecycle Safety.

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period.

15.4.2. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on an Overdose form and faxed to IQVIA Lifecycle Safety within 24 hours of the site becoming aware of the overdose. An overdose must be reported to IQVIA Lifecycle Safety even if the overdose does

not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed to IQVIA Lifecycle Safety). All study treatment-related dosing information must be recorded on the dosing CRF.

15.4.3. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator (or designee) should contact the IQVIA 24-hour emergency medical support number. Refer to the Study Reference Guide's Official Contact List for complete contact information.

15.4.3.1. Unblinding for Medical Emergency

In this study, emergency decoding will be made available to the Investigator and designated personnel at Biogen through IRT.

In a medical emergency when knowledge of the subject's treatment assignment may possibly influence the subject's clinical care, the Investigator may access the subject's treatment assignment by IRT. However, prior to unblinding, the Investigator can contact the IQVIA 24-hour emergency medical support number at PPD

The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, nor to personnel involved with the analysis and conduct of the study.

15.5. Contraception Requirements

For the purposes of this study, women of childbearing potential are defined as all women physiologically capable of becoming pregnant, UNLESS they meet one of the following conditions:

- Postmenopausal
  - 12 months of natural (spontaneous) amenorrhea without an alternative medical cause or 6 weeks after surgical bilateral oophorectomy with or without hysterectomy.
- Post hysterectomy.
- Female surgical sterilization (e.g., bilateral tubal ligation).

For the purposes of this study, highly effective contraception is defined as use of 1 of the following:

- For females of childbearing potential:
  - Established use of oral, injected, or implanted hormonal methods of contraception.
  - Placement of an intrauterine device or intrauterine system

  - Barrier methods of contraception with use of a spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide.
  - Male sexual partners underwent surgical sterilization with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate.

- For males:
  - Vasectomy with negative semen analysis at FU.
  - Use of condoms with spermicide.
  - Female sexual partners who underwent surgical sterilization (e.g., bilateral tubal ligation), are postmenopausal, are post-hysterectomy, or are using highly effective contraception as listed above for female subjects.

  For males and females of childbearing potential:

  True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies and FU on the outcome of the pregnancy in female subjects.
- Complete an SAE form for each SAE and fax it to Biogen (or designee) within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE FU information actively and persistently. FU information must be reported to Biogen (or designee) within 24 hours of the study site staff becoming aware of new information.

- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE FU information, if possible, until the event has resolved or become stable.
- Report SAEs to local EC/IRBs, as required by local law.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor (IQVIA) is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen (or designee) is to notify all appropriate regulatory authorities, central EC/IRBs, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Demography and Baseline Disease Characteristics

Demographics and baseline data will be summarized by treatment group with summary statistics (mean, standard deviation [SD], median, and range) or with frequency distributions.

16.2. Efficacy and Pharmacodynamics

16.2.1. Analysis Population

The intent-to-treat (ITT) population, defined as all subjects who were randomized and received at least 1 dose of study treatment (aducanumab or placebo), will be used for the efficacy analyses. Subjects will be analyzed in the groups to which they were randomized.

16.2.2. Methods of Analysis

16.2.2.1. General Considerations

Summary statistics will be presented. For continuous endpoints, summary statistics will generally include: number of subjects with data, mean, standard deviation, median, and range. For categorical endpoints, this will generally include: number of subjects randomized or dosed, number with data, and the percent of those with data in each category. Statistical testing for efficacy endpoints will be made between each aducanumab dose (high and low) and placebo. All statistical tests will be 2-sided.

16.2.2.2. Aducanumab Doses to be Evaluated

The following aducanumab doses as compared with placebo will be evaluated:

- Aducanumab high-dose (10 mg/kg in ApoE ε4 [including 6 mg/kg for subjects enrolled under protocol versions prior to Version 4 who do not have the opportunity to uptitrate to 10 mg/kg prior to completing Week 78 of the study] and 10 mg/kg in ApoE ε4 non-carriers).
- Aducanumab low-dose (3 mg/kg in ApoE ε4 carriers and 6 mg/kg in ApoE ε4 non-carriers).

In the event that the maximum dose (10 mg/kg) is terminated after the start of the study (Section 5.3.2) the definition of aducanumab high dose and aducanumab low dose will be modified as shown in Table 17. The dosing modification will be entirely based on interim analysis of outcomes that are independent of, and uninformative about, the treatment-related efficacy effect. Control of Type I error rate is thus maintained without a statistical adjustment for such adaptations [Chow and Chang 2011].

Table 17: Treatment Groups in the Event of High Dose Group Termination

High Dose Group(s) Terminated	Definitions of Revised Treatment (Low/High Dose) Groups for Comparison
ApoE ε4 carrier high-dose group (10 mg/kg) [including 6 mg/kg for subjects enrolled under versions prior to Version 4 who do not have the opportunity to uptitrate to 10 mg/kg prior to completing Week 78 of the study]	Low: ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg High: ApoE ε4 carrier 3 mg/kg and non-carrier 10 mg/kg
ApoE ε4 non-carrier high-dose group (10 mg/kg)	Low: ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg High: ApoE ε4 carrier 10 mg/kg and non-carrier 6 mg/kg
ApoE ε4 carrier high-dose group (10 mg/kg) AND ApoE ε4 non-carrier high-dose group (10 mg/kg)	ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg

16.2.2.3. Considerations for Multiple Comparison Adjustments

A sequential (closed) testing procedure will be used to control the overall Type I error rate due to multiple comparisons for the primary endpoint. The order of treatment comparisons is as follows: aducanumab high-dose versus placebo and aducanumab low-dose versus placebo. All comparisons after the initial comparison with $p > 0.05$ will not be considered statistically significant.

Secondary endpoints have been rank prioritized, in the order shown in Section 6. In order to control for a Type I error for the secondary endpoints, a sequential closed testing procedure will be used and will include both the order of the secondary endpoints and treatment comparisons. Specifically, for each of the secondary endpoints, a sequential (closed) testing procedure, as for the primary endpoint, will be used to control the overall Type I error rate due to multiple treatment comparisons. If statistical significance is not achieved for 1 or 2 comparisons, all endpoint(s) of a lower rank will not be considered statistically significant for 1 or 2, respectively.

16.2.2.4. Analysis of the Primary Endpoint

The population for the primary endpoint analysis will be subjects in the ITT population. A mixed model repeated measures (MMRM) model will be used as the primary analysis to analyze change from baseline CDR-SB using fixed effects of treatment, time, treatment-by-time interaction, baseline CDR-SB, baseline CDR-SB by time, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE ε4 status.

16.2.2.5. Analysis of the Secondary Endpoints

16.2.2.5.1. Change From Baseline to Week 78 in MMSE

The population for the analysis will be subjects in the ITT population. A MMRM model will be used as the primary analysis to analyze change from baseline MMSE using fixed effects of treatment, time, treatment-by-time interaction, baseline MMSE value, baseline MMSE by time interaction, AD symptomatic medication use at baseline, region, and laboratory ApoE ε4 status

16.2.2.5.2. Change From Baseline to Week 78 in ADAS-Cog 13

The population will be subjects in the ITT population. An MMRM model will be used as the primary analysis to analyze change from baseline ADAS-Cog 13 using fixed effects of treatment, time, treatment-by-time interaction, baseline ADAS-Cog 13, baseline ADAS-Cog 13 by time interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE ε4 status.

16.2.2.5.3. Change From Baseline to Week 78 in ADCS-ADL-MCI

The population will be subjects in the ITT population. An MMRM model will be used as the primary analysis to analyze change from baseline ADCS-ADL-MCI using fixed effects of treatment, time, treatment-by-time interaction, baseline ADCS-ADL-MCI, baseline ADCS-ADL-MCI by time interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE ε4 status.

16.2.2.6. Tertiary Endpoints Analysis

16.2.2.6.1. Placebo-Controlled Period

Where appropriate, an MMRM model will be used as the primary analysis to analyze change from baseline using fixed effects of treatment, time, treatment by time interaction, baseline value, baseline value by time interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE ε4 status.

Otherwise, an analysis of covariance may be used to analyze these exploratory endpoints or descriptive summary statistics may be presented.

16.2.2.6.2. Long-Term Extension Period

The endpoints for the LTE period are change from baseline over the placebo-controlled and LTE periods of the study. Analyses will be presented by treatment group in the LTE period using the placebo-controlled period baseline. Details of the analyses will be prespecified in the statistical analysis plan (SAP).

16.3. Pharmacokinetics

16.3.1. Analysis Population

The population for PK analysis is defined as all subjects who were randomized, were dosed with study treatment, and had at least 1 measurable aducanumab concentration in serum.

16.3.2. Method of Analysis

The serum concentrations and PK parameters of aducanumab will be summarized descriptively.

16.4. Additional Exploratory Analyses

Results of analyses of additional exploratory endpoints, if performed, may be documented separately, and details related to the analyses will not be described in the protocol.

16.5. Safety

16.5.1. Analysis Population

The safety population is defined as all subjects who were randomized and received at least 1 dose of study treatment (including placebo and aducanumab).

16.5.2. Methods of Analysis

All AEs, laboratory data, ECG, neurological and physical examinations and vital signs will be evaluated for safety.

16.5.2.1. Adverse Events

Only treatment-emergent adverse events (TEAEs) will be presented in the summary tables. Treatment emergent is defined as having an onset date that is on or after the start of study treatment, or as worsening after the start of study treatment.

Incidence of TEAEs will be summarized by treatment groups, overall, by severity, and by relationship to study treatment for the placebo-controlled period and up to 5 years of LTE period. The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

16.5.2.2. Clinical Laboratory Results

Laboratory data will be summarized using shift tables. Shifts from baseline to high/low status for hematology and blood chemistry parameters, and shifts from baseline to high/positive status for urinalysis will be presented. In addition, the shift from baseline to the maximum post-baseline value and the shift from baseline to the minimum post-baseline status will be presented for each laboratory test by treatment group. Also, summaries of laboratory values categorized based on common toxicity criteria grade will be created. Summary statistics for actual values and change from baseline will also be presented for quantitative laboratory data.

16.5.2.3. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities.

16.5.2.4. ECG

The number and percentage of subjects with shifts to categorical values (abnormal not AE, or abnormal AE) will be summarized by treatment group.

16.5.2.5. Columbia Suicide Severity Rating Scale

The C-SSRS data will be summarized by treatment group.

16.6. Immunogenicity Data

16.6.1. Analysis Population

The analysis population for immunogenicity is defined as all subjects in the safety population who have at least 1 post-dose sample evaluated for immunogenicity.

16.6.2. Methods of Analysis

Anti-aducanumab serum antibodies will be summarized using shift tables.

16.7. Interim Analyses

16.7.1. Interim Futility Analysis

An interim analysis for futility of the primary endpoint will occur after approximately 50% of the subjects have completed the Week 78 Visit (or discontinued). In order to maintain the treatment blind, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim futility analysis. This independent group will present the unblinded interim analysis to the IDMC. The IDMC may recommend terminating the study for futility if it is evident that the efficacy of aducanumab is unlikely to be achieved.

The futility criteria will be discussed in detail in the SAP.

16.7.2. Interim Superiority Analysis

An interim analysis for superiority may be performed after approximately 50% of the subjects have completed the Week 78 Visit (or discontinued). The O'Brien-Fleming boundary approach will be used for the analysis. In order to maintain the treatment blind in the event of this interim analysis, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim superiority analysis. The independent group will present the unblinded interim analysis to the IDMC. The aim of this interim analysis is to allow the possibility to demonstrate treatment effect early. The analysis will be discussed in detail in the SAP.

16.8. Sample Size Considerations

The study's sample size is based, in part, on results from a protocol-specified interim analysis from Study 221AD103, which included 1-year data from 1, 3, and 10 mg/kg treatment groups.

A sample size of 450 subjects per treatment group (1350 in total) was planned to have approximately 90% power to detect a true mean difference of 0.5 in change from baseline CDR-SB at Week 78 between the 2 treatment groups. This power calculation was based on a 2-sided t-test assuming equal variance with a final significance level of 0.05, an SD of 1.92, and a drop-out rate of 30%. The SD estimate of 1.92 for Week 78 reflected a 39% increase over the SD from the protocol-specified interim analysis of 1-year data.

The assumed true mean difference of 0.5 between the 2 treatment groups represents an approximately 25% reduction in the placebo mean change from baseline at Week 78 if the placebo mean change is estimated to be 2.

As defined in the prior versions of the protocol, the sample size for this study (and for the identically designed Study 221AD301) was reassessed in a blinded manner approximately 3 months before enrollment completion. At the time of this reassessment (November 2017), about 10.6% of the data was available on the primary endpoint from Study 221AD301 and Study 221AD302 combined; based on the pooled blinded data (i.e., treatment groups combined) from the 2 studies, the SD for the primary endpoint was estimated. As a result of this analysis, the sample size has been adjusted from 1350 to 1605 (450 to 535 per treatment) to assure adequate power to detect a mean treatment effect of 0.5.

17. ETHICAL REQUIREMENTS

Biogen, IQVIA, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated.

17.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

17.2. Ethics Committee/Institutional Review Board

The Investigator must obtain EC/IRB approval of the protocol, ICF, and other required study documents prior to starting the study. Biogen will submit documents on behalf of the investigational sites worldwide in compliance with local requirements.

If the Investigator makes any changes to the ICF, Biogen must approve the changes before the ICF is submitted to the EC. A copy of the approved ICF must be provided to Biogen. After approval, the ICF must not be altered without the agreement of the relevant EC and Biogen.

It is the responsibility of the Investigator(s) to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

Biogen must receive a letter documenting EC/IRB approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the EC/IRB at required intervals and not less than annually.

At the completion or termination of the study, the investigational site must submit a close-out letter to the EC/IRB and Biogen.

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations. Subjects can complete the neurocognitive scales (CDR, MMSE, and RBANS) as well as ApoE genotyping as an initial optional screening under a separate consent process. If the subject meets inclusion criteria for these 3 scales, the full consent process must be completed prior to the administration of further screening assessments.

Subjects may also proceed directly to the full consent process that would allow the administration of all screening assessments.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject (or the subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

Subjects will be informed that their race and/or ethnicity will be collected and will be used during analysis of study results (only in countries where permitted by local law/regulation).

A copy of the signed and dated ICF must be given to the subject, caregiver and/or legally authorized representative. The signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the subject's medical record.

17.4. Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., Protected Health Information authorization in North America).

The subject will not be identified by name in the CRF or in any study reports and these reports will be used for research purposes only. Biogen, its partner(s) and designee(s), EC/IRBs, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

During the study, subjects' race and/or ethnicity will be collected (only in countries where permitted by local law/regulation). These data may be used in the analysis of the safety, efficacy, and/or pharmacokinetic profile of the study treatment. It is unknown if the potency or effects of the study treatment are influenced by race or ethnicity.

17.5. Compensation for Injury

Biogen maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in Biogen or its partner[s]) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

Biogen will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by Biogen. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

During and/or after completion of the study, quality assurance officers named by Biogen or the regulatory authorities may wish to perform onsite audits. The Investigator will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested.

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor(s) will visit the Investigator(s) at regular intervals during the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contract(s) between the institution, Investigator, and Biogen.

18.5. Publications

Details are included in the clinical trial agreement for this study.

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

19.1.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of SAE reports. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or randomized, the IRT vendor will provide each study site with appropriate training, access rights, and a user manual.

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a web-based electronic data capture (EDC) tool developed by IQVIA and configured by the EDC vendor.

19.1.4. Central Laboratories for Laboratory Assessments

Biogen has selected a central laboratory service to perform all standard hematology, blood chemistry, and urinalysis testing for the study. This central laboratory will also receive, track, and ship all urine, blood, CSF samples, and DNA for specialized ApoE ε4 genotyping, PK, biomarker, and ADA testing, including aliquots from these samples retained as backup in case original samples are lost or not evaluable. Blood samples collected for future DNA testing will be processed to purify DNA and stored by the central laboratory.

Laboratories performing specialized testing will be identified in regulatory documentation. These laboratories will use appropriately validated or qualified assays to test study samples.

19.1.5. Central Facility for Other Assessments

A central imaging laboratory has been selected by Biogen to read and interpret all MRIs for this study within the timeframe specified in the procedural manual for MRI. In cases of ARIA-E and ARIA-H, the central imaging laboratory must expedite notification to the PI and the Sponsor. For the purposes of study conduct, the MRI interpretations from the central reader will prevail over those from the local radiologist.

The central imaging laboratory will also collect PET scans and assess the screening scan for eligibility criteria.

19.1.6. Neurocognitive Assessments

Biogen selected a rater management group to establish rater qualification, study-specific training, and oversight. The study raters are required to complete qualifications steps and required training prior to administering study assessments. The rater management group will oversee the assessments per project-specific plans.

19.2. Study Committees

19.2.1. Advisory Committee

An advisory committee will be formed to provide scientific and medical direction for the study and to oversee the administrative progress of the study. The advisory committee will meet periodically to monitor subject accrual and oversee study conduct, including advising on study design and execution. The advisory committee will be blinded to subject treatment assignments during the study.

Members of the advisory committee will include external experts in Alzheimer's disease. Biogen will designate one of the participating external experts to be the chairperson of the advisory committee.

19.2.2. Independent Data Monitoring Committee

The IDMC will be formed to review ongoing safety and tolerability data. Members of the IDMC will not be allowed to participate as Investigators in this study. The IDMC will review safety data on an ongoing basis to ensure safe and proper treatment of subjects. The IDMC, based on the nature, frequency, and/or severity of an AE(s) may recommend protocol modification(s), dose suspension, dose termination or study termination. An IDMC charter will provide full guidance on the function and practices to be followed by the IDMC.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the EC/IRB and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the EC/IRB before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, Biogen may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Sections 17.2 and 17.3).

19.4. Ethics Committee/Institutional Review Board Notification of Study Completion or Termination

Where required, the regulatory authorities and EC/IRBs must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator must notify Biogen of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

Biogen will designate one or more of the participating Study Investigators as a signatory for the study report. This determination will be made by several factors including but not limited to the Investigator's experience and reputation in the studied indication, the Investigator's contribution to the study in terms of design, management, and/or subject enrollment, or by other factors determined to be relevant by Biogen.

20. REFERENCES

Albert MS, DeKosky ST, Dickson D, 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(3):270-9.

Alzheimer's Disease International. World Alzheimer Report 2014: Dementia and risk reduction. London: Alzheimer's Disease International (ADI); 2014.

Chow S, Chang M. Adaptive Design Methods in Clinical Trials, Second Edition. Second Edition ed. Boca Raton, FL: Chapman and Hall/CRC; 2011.

Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol. 2010;9(11):1118-27.

Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 2014;13(6):614-29.

Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002;297(5580):353-6. Epub 2002 Jul 20.

Hock C, Konietzko U, Streffer JR, et al. Antibodies against beta-amyloid slow cognitive decline in Alzheimer's disease. Neuron. 2003;38(4):547-54. Epub 2003/05/27.

Jack CR, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013;12(2):207-216.

Koffie RM, Meyer-Luehmann M, Hashimoto T, et al. Oligomeric amyloid beta associates with postsynaptic densities and correlates with excitatory synapse loss near senile plaques. Proc Natl Acad Sci U S A. 2009;106(10):4012-7.

Kuchibhotla KV, Goldman ST, Lattarulo CR, et al. Abeta plaques lead to aberrant regulation of calcium homeostasis in vivo resulting in structural and functional disruption of neuronal networks. Neuron. 2008;59(2):214-25.

Kumar-Singh S, Pirici D, McGowan E, et al. Dense-core plaques in Tg2576 and PSAPP mouse models of Alzheimer's disease are centered on vessel walls. American Journal of Pathology. 2005;167(2):527-43. Epub 2005/07/29.

Lenderking WR, Steenrod A, Rüdell K, et al. Options for Evaluating Treatment Benefit in MCI and Prodromal Alzheimer's Disease: Content Validity of the Perceived Deficits Questionnaire (PDQ) in Patients with Early Symptoms of Cognitive Decline. Advances in Alzheimer's Disease. 2014;3:1-10. Epub March 2014.

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. Alzheimer's and Dementia. 2011;7(3):263-269.

Meyer-Luehmann M, Spires-Jones TL, Prada C, et al. Rapid appearance and local toxicity of amyloid-beta plaques in a mouse model of Alzheimer's disease. Nature. 2008;451(7179):720-4.

Morris JC, Blennow K, Froelich L, et al. Harmonized diagnostic criteria for Alzheimer's disease: recommendations. J Intern Med. 2014;275(3):204-13.

Ostrowitzki S, Deptula D, Thurfjell L, et al. Mechanism of amyloid removal in patients with Alzheimer disease treated with gantenerumab. Arch Neurol. 2012;69(2):198-207. Epub 2011 Oct 10.

Pfeifer M, Boncristiano S, Bondolfi L, et al. Cerebral hemorrhage after passive anti-Abeta immunotherapy. Science. 2002;298(5597):1379. Epub 2002/11/16.

Racke MM, Boone LI, Hepburn DL, et al. Exacerbation of cerebral amyloid angiopathy-associated microhemorrhage in amyloid precursor protein transgenic mice by immunotherapy is dependent on antibody recognition of deposited forms of amyloid beta. J Neurosci. 2005;25(3):629-36. Epub 2005/01/22.

Rozkalne A, Spires-Jones TL, Stern EA, et al. A single dose of passive immunotherapy has extended benefits on synapses and neurites in an Alzheimer's disease mouse model. Brain Res. 2009;1280:178-85.

Sperling RA, Jack Jr CR, Black SE, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: Recommendations from the Alzheimer's Association Research Roundtable Workgroup. Alzheimers Dement. 2011;7(4):367-385.

Spires-Jones TL, Mielke ML, Rozkalne A, et al. Passive immunotherapy rapidly increases structural plasticity in a mouse model of Alzheimer disease. Neurobiol Dis. 2009;33(2):213-20.

Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke. 2001;32(6):1318-22.

Weller RO, Subash M, Preston SD, et al. Perivascular drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and Alzheimer's disease. Brain Pathol. 2008;18(2):253-66.

Wilcock DM, Colton CA. Immunotherapy, vascular pathology, and microhemorrhages in transgenic mice. CNS Neurol Disord Drug Targets. 2009;8(1):50-64. Epub 2009/03/12.

Winkler DT, Bondolfi L, Herzig MC, et al. Spontaneous hemorrhagic stroke in a mouse model of cerebral amyloid angiopathy. J Neurosci. 2001;21(5):1619-27. Epub 2001/02/27.

21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease", and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

ENGAGE

221AD302

Statistical Analysis Plan

Placebo-Controlled Period

STATISTICAL ANALYSIS PLAN
Placebo-Controlled Period

Product Studied: Aducanumab
Protocol Number: 221AD302

A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease

Protocol Version: Version 6.0
Date of Protocol: 28 Jun 2018

Date of Statistical Analysis Plan: 11 Sep 2018, Final V1.0

Written By:	PPD	12 Sep 2018 Date
		12 Sep 2018 Date
Approved By:		12 Sep 2018 Date
		12 Sep 2018 Date
		12 Sep 2018 Date

Table of Contents

List of Abbreviations

Aβ	β-amyloid
AD	Alzheimer's disease
ADAS-Cog 13	Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items)
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment version)
ADNI	Alzheimer's Disease Neuroimaging Initiative
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
ApoE ε4	apolipoprotein E4
ApoE ε4+	apolipoprotein E4 carrier
ApoE ε4-	apolipoprotein E4 non-carrier
ARIA	amyloid related imaging abnormalities
ARIA-E	amyloid related imaging abnormality-edema
ARIA-H	amyloid related imaging abnormality-hemorrhage or superficial siderosis
ASL-MRI	arterial spin labeling magnetic resonance imaging
AST	aspartate aminotransferase
BL	baseline
BLQ	below the limit of quantification
BMI	body mass index
bpm	beats per minute
BUN	blood urea nitrogen
CAM	Caregiver Assessment Measure
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CIR	copy increment from reference
C_{max}	observed maximum serum aducanumab concentration
C_{min}	observed minimum serum aducanumab concentration
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAT	Common Toxicity Criteria for Adverse Events
CV	coefficient of variation
EAIR	exposure-adjusted incidence rate
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D	EuroQol health status measure
EQ-5D (IR-I)	EuroQol health status measure, informant reported on informant's own health status
EQ-5D (IR-S)	EuroQol health status measure, informant reported on subject

EQ-5D (SR)	EuroQol health status measure, subject self-reported
FU	Follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl-transferase
HCP	health care professional
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IXRS	Interactive Voice/Web Response System
LDH	lactate dehydrogenase
LMCI	late mild cognitive impairment
LTE	long-term extension
LOCF	last observation carried forward
MCI	mild cognitive impairment
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-model repeated measures
MMSE	Mini-Mental State Examination
MOCA	Montreal Cognitive Assessment
mPDQ-20	Perceived Deficits Questionnaire-20 modified version
MRI	magnetic resonance imaging
NIA-AA	National Institute on Aging-Alzheimer's Association
NPI-10	Neuropsychiatric Inventory-10
PCS	potentially clinically significant
PET	positron emission tomography
pH	potential of hydrogen
PI	Principal Investigator
PK	pharmacokinetic(s)
PMM	pattern mixture model
PP	per-protocol
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
ROI	region of interest
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
SUVR	standard uptake value ratio
TEAE	treatment-emergent adverse event
tf-fMRI	task free functional MRI
ULN	upper limit of normal
US	United States
WHO	World Health Organization

1 DESCRIPTION OF OBJECTIVES AND ENDPOINTS

1.1 Primary Objective and Endpoint

The primary objective of this study is to evaluate the efficacy of monthly doses of aducanumab in slowing cognitive and functional impairment as measured by changes in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score as compared with placebo in subjects with early Alzheimer's Disease (AD).

The primary endpoint that relates to this objective is change from baseline in CDR-SB score at Week 78.

1.2 Secondary Objectives and Endpoints

The secondary objectives of this study are:

- To assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by the Mini-Mental State Examination (MMSE).
- To assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by Alzheimer's Disease Assessment Scale-Cognitive Subscales (13 items) [ADAS-Cog 13].
- To assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI].

The secondary endpoints are:

- Change from baseline in MMSE score at Week 78.
- Change from baseline in ADAS-Cog 13 score at Week 78.
- Change from baseline in ADCS-ADL-MCI score at Week 78.

1.3 Tertiary Objectives and Endpoints

1.3.1 Tertiary Objectives

Safety and Tolerability

- To assess the safety and tolerability of monthly doses of aducanumab.
- To assess the immunogenicity of aducanumab.

Biomarker/Efficacy/Quality of Life

- To assess the effect of aducanumab on cerebral amyloid plaque content as measured by amyloid positron emission tomography (PET) imaging (in a subset of approximately 400 subjects).
- To assess the effect of aducanumab on behavior as measured by the Neuropsychiatric Inventory-10 (NPI-10).
- To assess the effect of aducanumab on subject health status, measured by EuroQol health status measures (EQ-5D [informant-rated and subject self-reported]).
- To assess the effect of aducanumab on subject self-reported cognitive function, measured by the modified Perceived Deficits Questionnaire-20 (mPDQ-20).
- To assess the correlation between primary endpoint and cerebral amyloid plaque content as measured by PET imaging.

Pharmacokinetics

- To collect and characterize the pharmacokinetic (PK) parameters of aducanumab in serum

1.3.2 Tertiary Endpoints

Safety and Tolerability

- Incidence of all adverse events (AEs) and serious adverse events (SAEs).
- Brain magnetic resonance imaging (MRI) findings including incidence of amyloid related imaging abnormality-edema (ARIA-E) and amyloid related imaging abnormality-hemorrhage or superficial siderosis (ARIA-H).
- Clinical laboratory shifts in reported values.
- Clinically significant changes in vital sign measurements and electrocardiograms (ECGs).
- Incidence of anti-aducanumab antibodies in serum.

Biomarkers/Efficacy/Quality of Life

- Change from baseline in amyloid PET signal at Week 26 (in a subset of sites and subjects).
- Change from baseline in amyloid PET signal at Week 78 (in a subset of sites and subjects).
- Change from baseline in NPI-10 score at Week 78.
- Change from baseline in subject-self-reported EQ-5D index score at Week 78.
- Change from baseline in informant-rated subject EQ-5D index score at Week 78.
- Change from baseline in mPDQ-20 at Week 78.
- Correlation between the primary endpoint and cerebral amyloid plaque content as measured by PET imaging over time.

Pharmacokinetics:

- Serum concentrations and PK parameters of aducanumab.

1.4 Additional Exploratory Objectives and Endpoints

1.4.1 Additional Exploratory Objectives

Biomarker

- To assess the effect of aducanumab on various morphometric measures in certain brain areas as measured by MRI.
- To assess the effect of aducanumab on functional connectivity by task free functional MRI (tf-fMRI) (where available, in a subset of sites and subjects).
- To assess the effect of aducanumab on cerebral blood flow by arterial spin labeling (ASL)-MRI (where available, in a subset of sites and subjects).
- To assess the effect of aducanumab on disease- or treatment-related biomarkers in cerebrospinal fluid (CSF), which may include, but are not limited to, amyloid and tau proteins (in a subset of subjects).
- To assess the effect of aducanumab on disease- or treatment-related biomarkers in blood, which may include, but are not limited to, amyloid and tau proteins.
- To assess the effect of aducanumab on tau pathology by tau PET imaging (where available, in a subset of sites and subjects).

Health Outcomes

- To assess the effect of aducanumab on the informant/care partner's own health status, measured by the EQ-5D.
- To assess the effect of aducanumab on caregiver burden as measured by the Caregiver Assessment Measure (CAM).

1.4.2 Additional Exploratory Endpoints

Biomarkers

- Change from baseline in whole brain volume, hippocampal volume, ventricular volume, and cortical gray matter volume measured by MRI over time.
- Change from baseline in functional connectivity as measured by tf-fMRI over time (where available, in a subset of sites and subjects).
- Change from baseline in cerebral blood flow as measured by ASL-MRI over time (where available, in a subset of sites and subjects).
- Change from baseline in CSF biomarkers, which may include, but are not limited to, amyloid or tau proteins at Week 78 (in a subset of subjects).
- Change from baseline over time in blood biomarkers, which may include, but are not limited to, amyloid or tau proteins.
- Change from baseline in tau PET signal at Week 78 (where available, in a subset of sites and subjects).

Health Outcomes

- Change from baseline in informant/care partner's own EQ-5D index-score at Week 78.
- Changes on the CAM over time.

2 STUDY DESIGN

2.1 Study Overview

Study 221AD302 (EMERGE) is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects with early AD, including mild cognitive impairment (MCI) due to AD and a subset of mild AD, followed by an optional dose-blinded long-term extension (LTE) period of up to 5 years. Approximately 1605 subjects will be enrolled across approximately 150 centers globally. The primary study objective is to evaluate the efficacy of monthly doses of aducanumab on the CDR-SB relative to placebo. Secondary objectives include assessment of the effect of monthly doses of aducanumab on clinical progression as compared to placebo. The safety of monthly doses of aducanumab will also be evaluated.

Table 1: Dosing Scheme for Aducanumab by Treatment Group and ApoE ε4 Carrier Status: Placebo-Controlled Period

Dose (every 4 weeks)		**1**	**2**	**3**	**4**	**5**	**6**	**7 to 20**
Treatment Group	**Treatment Group Stratified by ApoE Status[2]**	**Dose (mg/kg)**						
High Dose	**High Dose - ApoE ε4 (+)**	1	1	3	3	6	6	10[1]
	High Dose - ApoE ε4 (-)	1	1	3	3	6	6	10
Low Dose	**Low Dose - ApoE ε4 (+)**	1	1	3	3	3	3	3
	Low Dose - ApoE ε4 (-)	1	1	3	3	3	3	6
Placebo	**Placebo - ApoE ε4 (+)**	saline						
	Placebo - ApoE ε4 (-)	saline						

[1] 10 mg/kg is the target dose for all ApoE ε4 carriers assigned to the aducanumab high-dose group. Subjects enrolled under protocol versions 1-3 and assigned to the previous high-dose of 6 mg/kg will be titrated to 10 mg/kg upon receipt of at least 2 doses at 6 mg/kg.

[2] ApoE ε4 status recorded in the Interactive Voice/Web Response System (IXRS).

Subjects will be randomized in a 1:1:1 ratio to 1 of the 3 treatment groups: aducanumab high dose, aducanumab low dose and placebo, with stratification based upon their apolipoprotein E4 (ApoE ε4) carrier status (carrier/non-carrier) and site. During the placebo-controlled period, subjects will receive infusions of aducanumab or placebo approximately every 4 weeks for approximately 18 months (a total of 20 doses). Dose levels may be different in the same treatment group based upon subjects' ApoE ε4 carrier status, and specifically, ApoE ε4

carriers will receive placebo, aducanumab 3 mg/kg, or aducanumab 10 mg/kg whereas ApoE ε4 non-carriers will receive placebo, aducanumab 6 mg/kg, or aducanumab 10 mg/kg. Aducanumab will be titrated for up to 6 doses prior to reaching the target dose as shown in Table 1 and Figure 1. Note: As of Protocol Version 4, 10 mg/kg is the target dose for all ApoE ε4 carriers in the high-dose group. ApoE ε4 carriers who were randomized to the high dose group when the target dose was 6 mg/kg (under protocol versions prior to Version 4) must have received 2 or more doses at 6 mg/kg prior to being titrated up to 10 mg/kg.

At the end of the double-blind, placebo-controlled treatment period, subjects who meet the extension entry criteria may enter a long-term safety and efficacy extension period, with all subjects receiving aducanumab approximately every 4 weeks (up to a total of 65 doses over 5 years). The treatment group for the LTE period will be assigned at the same time as the randomization for the placebo-controlled period, regardless of whether a subject entering the LTE period or not. Subjects who are assigned to the placebo group during the placebo-controlled period will be assigned to 1 of 2 active treatment groups in a 1:1 ratio (aducanumab low dose: aducanumab high dose) and randomization will be stratified by their ApoE ε4 carrier status; for those who enter the LTE period, aducanumab will be titrated for up to 6 doses prior to reaching the target dose following the same schedule described for the placebo-controlled period. Subjects who are assigned to either aducanumab low dose or aducanumab high dose group in the placebo-controlled period will continue in the same treatment group for the LTE period; those who enter the LTE period will maintain the dosing scheme outlined in the protocol at the time of transition from the placebo-controlled period to the LTE period (e.g. subjects who are on stable dosing in the placebo-controlled period will continue on the same dose, subjects who are on a titration regimen during the transition will continue to titrate into the LTE period, and ApoE ε4 carrier subjects who are enrolled in the LTE and randomized to the high-dose group prior to implementation of version 4 of the protocol will be allowed to titrate to 10 mg/kg).

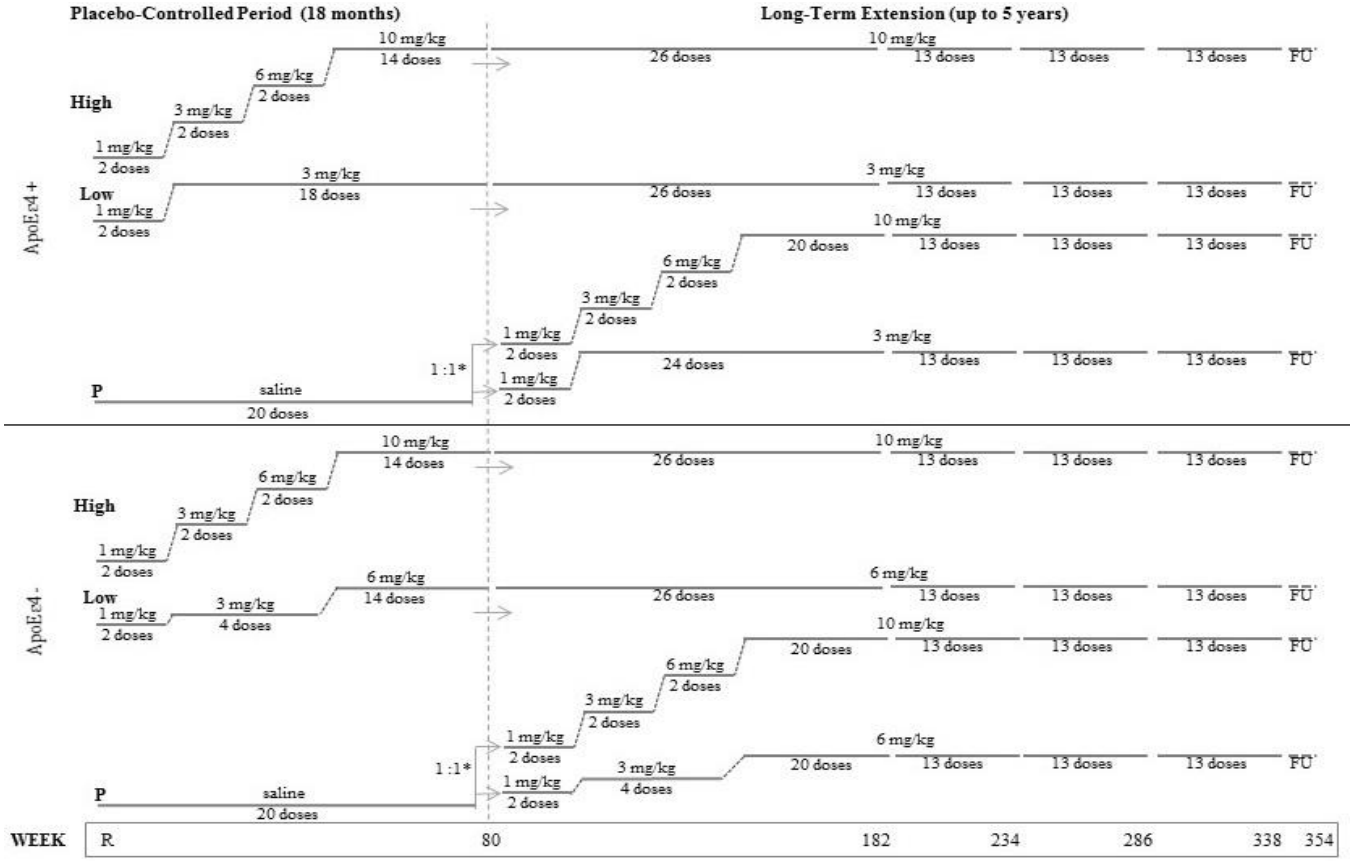
Individual dose adjustments may be implemented in subjects who develop amyloid related imaging abnormalities (ARIA). See Protocol Section 7.2.1.

The total duration of study participation for each subject only participating in the placebo-controlled period of the study will be up to approximately 102 weeks, including a series of Screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, and a safety follow-up (FU) period of approximately 18 weeks after the final dose. The total duration of study participation for each subject participating in the placebo-controlled period and the LTE period will vary and be up to approximately 362 weeks, including a series of Screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, a 4-week FU period, a 256-week aducanumab dose-blind treatment period, and a safety FU period of approximately 18 weeks after the final dose.

Investigators, study site staff (except for the designated unblinded pharmacist/technician), and study subjects will be blinded to the subjects' randomized treatment assignment for the placebo-controlled period. During the LTE period, investigators and subjects will remain blinded to the treatment assignment in the placebo-controlled period and the aducanumab dose for the LTE period.

2.2 Study Schematic

Figure 1: Study Design



ApoE ε4 +/- = apolipoprotein E4 positive/negative; FU = follow-up; P = placebo; R = randomization date.
*Subjects who are assigned to placebo during the placebo-controlled period are randomized in a 1:1 ratio to high and low dose aducanumab treatment (stratified by their ApoE ε4 carrier status) for the long-term extension period on Study Day 1.

2.3 Schedule of Events

See Protocol Section 4.2.

3 SAMPLE SIZE JUSTIFICATION

The study's sample size is based, in part, on results from a protocol-specified interim analysis from Study 221AD103 which included 1 year data from 1, 3 and 10 mg/kg treatment groups.

A sample size of 450 subjects per treatment group (1350 in total) was planned to have approximately 90% power to detect a true mean difference of 0.5 in change from baseline CDR-SB at Week 78 between the 2 treatment groups. This power calculation was based on a 2-sided t-test assuming equal variance with a final significance level of 0.05, a standard deviation (SD) of 1.92 and a drop-out rate of 30%. The SD estimate of 1.92 for Week 78 reflected a 39% increase over the SD from the protocol-specified interim analysis of 1-year data.

The assumed true mean difference of 0.5 between the 2 treatment groups represents an approximately 25% reduction in the placebo mean change from baseline at Week 78 if the placebo mean change is estimated to be 2.

As defined in the protocol, the sample size for this study (and for the identically designed Study 221AD301) was reassessed in a blinded manner in November 2017 (approximately 3 months before enrollment completion and with about 10.6% of the data available on the primary endpoint from Studies 221AD301 and 221AD302 combined). At this timepoint, the SD of the primary endpoint was estimated based on the pooled blinded data from two studies using a modified version of Gould-Shih simple-adjustment one sample variance (Zucker et al. 1999):

$$s_{adj}^2 = s_{os}^2 - \frac{2N}{9(N-1)}\delta^2,$$

where N denotes the number of subjects included in the analysis for blinded sample size re-estimation (subjects with both baseline and Week 78 CDR-SB available at the time of sample size re-estimation), δ is the assumed true treatment effect (same treatment effect assumed for both the high dose group and low dose group in this analysis), and s_{os}^2 is the unadjusted one sample variance of the primary endpoint estimate from the pooled blinded data.

As a result of this analysis, the sample size has been increased from 1350 to 1605 (450 to 535 per treatment group) to assure adequate power for detecting a mean treatment effect of 0.5.

4 STATISTICAL ANALYSIS METHODS

4.1 General Considerations

This statistical analysis plan (SAP) only covers the analyses for the primary, secondary and tertiary objectives for the placebo-controlled portion of the study. Hereafter, the placebo-controlled portion of the study will be referred to as "the study" in the rest of this SAP (e.g.,

completion of the study means completion of the placebo-controlled portion). A separate SAP will be prepared for the analyses of the LTE period and integrated analyses across both portions of the study. The analyses of additional exploratory endpoints will be documented separately.

Summary tables will be presented using descriptive summary statistics. For continuous variables, summary statistics will generally include: number of subjects with data, mean, standard deviation, median, 25% percentile, 75% percentile, minimum and maximum. For categorical variables, this will generally include: number of subjects randomized or dosed, number with data, and the percent of those with data in each category.

There are two types of analysis displays for tables: by treatment group (analysis display A in Appendix 6.1) and by treatment group stratified by ApoE status (analysis display B in Appendix 6.1; here ApoE status refers to the status recorded in IXRS [see Table 1 for correspondence between treatment groups and treatment groups stratified by ApoE status]). The analysis display for each analysis will be defined in each section. All the listings will be presented by treatment group stratified by ApoE status, unless otherwise specified.

Unless otherwise specified, baseline value is defined as the most recent non-missing measurement collected prior to the first dose. Change from baseline will be defined as post-baseline value minus baseline value.

Unless stated otherwise, all statistical tests will be 2-sided with statistical significance level of 0.05.

The statistical software, SAS® will be used for all summaries and analyses.

4.1.1 Analysis Population

- Intent-to-treat (ITT) population:
  The Intent-to-treat population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo).

- Per-protocol (PP) population:
  The per-protocol population is defined as all subjects in the ITT population and also
  - had no violations of the following inclusion criteria:
    - Must have at least 6 years of education or work experience to exclude mental deficits other than MCI or mild AD;
    - Must have a positive amyloid PET scan;
    - Must have:
      - A CDR-Global Score of 0.5;
      - A Repeatable Battery for Assessment of Neuropsychological Status (RBANS) score of 85 or lower indicative of objective cognitive impairment (based upon the Delayed Memory Index score);
      - An MMSE score between 24 and 30 (inclusive).
  - had at least 14 infusions.
  - did not make any change to concomitant AD symptomatic medications during the study.

- ^{18}F-florbetapir amyloid PET analysis population:
  The ^{18}F-florbetapir amyloid PET analysis population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo), used ^{18}F-florbetapir ligand for amyloid PET scan, and had an evaluable baseline amyloid PET SUVR value for the composite region-of-interest using cerebellum as the reference region.

- ^{18}F-flutemetamol amyloid PET analysis population (applicable only to Japan):
  The ^{18}F-flutemetamol amyloid PET analysis population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo), used ^{18}F-flutemetamol ligand for amyloid PET scan, and had an evaluable baseline amyloid PET SUVR value for the composite region-of-interest using cerebellum as the reference region.

- Safety population:
  The safety population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo). It is the same population as the ITT population.

- Safety MRI population:
  The safety MRI population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo) and had at least one post-baseline MRI assessment.

- PK analysis population:
  The PK analysis population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo) and had at least one measurable aducanumab concentration in serum.

- Immunogenicity population:
  The analysis population for immunogenicity is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo) and had at least one post-dose sample evaluable for immunogenicity.

4.2 Background Characteristics

The summaries in this section will be based on the ITT population. Unless otherwise specified, summary tables will be presented by treatment group (analysis display A in Appendix 6.1) and by treatment group stratified by ApoE status (analysis display B in Appendix 6.1; here ApoE status refers to the status recorded in IXRS [see Table 1 for correspondence between treatment groups and treatment groups stratified by ApoE status]). All the listings will be presented by treatment group stratified by ApoE status, unless otherwise specified.

4.2.1 Accounting of Subject

Disposition of subjects will be summarized and the summary data will include number (%) of subjects randomized and dosed, number (%) of subjects who completed the treatment/study, and number (%) of subjects who discontinued treatment and/or withdrew from study. For subjects who discontinued treatment and/or withdrew from study, the reasons for discontinuation and/or withdrawal, and days on treatment and days on study will be summarized and listed. The number of subjects discontinuing treatment prior to each scheduled clinical efficacy assessment will be summarized (presented by treatment group), i.e., the number of subjects discontinuing treatment between Day 1 and Week 26, the number of subjects discontinuing treatment between Week 26 and Week 50 visit, etc. A similar summary will be done for subjects who withdrew from study (presented by treatment group). Time to treatment discontinuation and time to study withdrawal will be displayed by Kaplan-Meier plot (presented by treatment group).

Number of subjects in each analysis population will be summarized. Number of subjects dosed will be summarized by region, country and site. In addition, number of subjects who completed the treatment/study will be summarized by region and country (presented by treatment group).

The categorization of region is based not only on consideration of geography but also on type of health care system and access to health care in each country. This region category will be used in all analysis, including the demographics, the covariate in statistical models and subgroup analysis. The categories for regions will be:

- Region 1: United States (US);
- Region 2: European countries (including Belgium, Finland, France, Germany, Italy, Netherlands, Poland, Spain, Sweden and Switzerland), plus Canada;
- Region 3: Asia countries (including Japan).

4.2.2 Demographics and Baseline Characteristics

The demographic data including age, gender, ethnicity, race, height, weight, and body mass index (BMI) will be summarized. Age will also be categorized and presented using the following two groupings: <50, 50-60, 61-70, 71-80, 81-85, >85 years, and ≤ 64, 65-74, ≥ 75.

Summary of the baseline characteristics of AD includes laboratory ApoE ε4 status (carrier or non-carrier), baseline clinical stage (MCI due to AD or mild AD), baseline clinical assessment including RBANS delayed memory index, CDR global score, CDR-SB, CDR cognitive subscore, CDR functional subscore, MMSE, ADAS-Cog 13, ADCS-ADL-MCI, number of years of formal education, number of years since first AD symptom, number of years since diagnosis of AD, AD treatment use that was stopped prior to entering the study (yes or no) and AD symptomatic medication use at baseline (yes or no; see Section 4.2.3 for definition of AD symptomatic medication use at baseline). ApoE ε4 carrier will be further classified as homozygote and heterozygote. MMSE will also be categorized by the following subgroups: <24, 24-26, 27-30. Subject listings will be generated for demographics and baseline characteristics.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number (%) of subjects with history (including both ongoing and not ongoing medical conditions) will be summarized by system organ class and preferred term. A listing of medical history will be generated.

Previous therapies for the treatment of AD stopped prior to entering the study, total duration of previous therapies and reason for stopping treatment will be summarized (presented by treatment group). A listing of previous therapies will also be generated.

4.2.3 Concomitant Medications and Non-Drug Therapies

All concomitant medications will be coded using the World Health Organization (WHO) medication dictionary. All concomitant non-drug therapies will be coded using the MedDRA dictionary. A concomitant medication/therapy will be defined as any therapy that was taken on or after the day of the first dose of study drug. This includes therapies that start prior to the initiation of the first dose if their use continues on or after the date of first dose. To define concomitant use for therapies with missing start or stop dates, the following additional criteria will be used:

- if both the start and stop dates of a therapy are missing, that therapy will be considered concomitant.
- if the start date of a therapy is missing and the stop date of that therapy fall on or after the date of the first dose, that therapy will be considered concomitant.
- if the start date of a therapy is prior to the date of the first dose and the stop date of that therapy is missing and the therapy is listed as continuing, that therapy will be considered concomitant, or
- if the start date of a therapy is prior to the date of the first dose and the stop date of that therapy is missing and the therapy is not listed as continuing, that therapy will be considered non-concomitant.

For a therapy with a partial start date, the year/month of the therapy date will be compared to that of the first dosing date to determine whether the therapy is concomitant.

The number (%) of subjects taking concomitant medication and non-drug therapies will be summarized. Non-drug therapies will be presented by treatment group. Concomitant medications and non-drug therapies will be listed.

AD symptomatic medications taken concomitantly at baseline are defined as AD symptomatic medications that were being taken at the time of the first dose, i.e., started prior to the first dose and continued until after the first dose. The number (%) of subjects taking AD symptomatic medications concomitantly at baseline will be summarized. In addition, number of subjects using Cholinesterase inhibitors only, Memantine only, or both at baseline will be summarized. Subjects who have any change in AD symptomatic medications after the initiation of study treatment will be summarized by the timing of change, i.e., the number of subjects changing between Day 1 and Week 26, the number of subjects changing between Week 26 and Week 50, etc. The summary for AD symptomatic medication use during study

will be presented by treatment group. The start and stop date of AD symptomatic medication will be listed for these subjects.

4.2.4 Protocol Deviations

Protocol deviations identified during site monitoring will be captured in a Protocol Deviation log and categorized as major or minor deviations based on Protocol Deviation Classification (see Appendix 6.2). The major protocol deviations will be summarized (presented by treatment group). Listings will be generated for the major and minor protocol deviations, respectively. A listing will be generated for subjects with incorrect stratification ApoE status, i.e., treatment stratification ApoE ε4 status in IXRS different from the laboratory ApoE ε4 status.

4.2.5 Study Drug Exposure and Study Drug Compliance

A summary table of study drug exposure and compliance will be provided. Number of infusions (aducanumab or placebo) received will be summarized as a categorical variable (categories as integers from 1 to 20, and 1-5, 6-10, 11-15, and 15-20) as well as a continuous variable. Number of weeks on study treatment (aducanumab or placebo), calculated as (date of last dose – date of first dose + 29)/7, will be summarized as a categorical variable (every 8 weeks from 0 to >= 72 weeks) as well as a continuous variable. Percentage of study treatment taken up to the last dose, calculated as (the actual number of infusions / by the number of infusions a subject is expected to take until the date of last infusion)*100, will be summarized as a continuous variable. This table will be presented by treatment group.

Due to the use of titration regimen in the study and possible dose reduction due to ARIA, another summary table will be provided including the following information: number of total infusions (categories of 1-5, 6-10, 11-15, and 15-20) as well as a continuous variable, number of infusions at each dose level (1 mg/kg, 3 mg/kg, 6 mg/kg and 10 mg/kg, respectively) summarized as a categorical variable as well as a continuous variable, number of subjects with dose increase (placebo to 1 mg/kg, 1 to 3 mg/kg, 3 to 6 mg/kg and 6 to 10 mg/kg, respectively), number of subjects with dose reduction (1 mg/kg to placebo, 3 to 1 mg/kg, 6 to 3 mg/kg and 10 to 6 mg/kg, respectively), maximum dose level received, and cumulative dose (as a continuous variable). This table will be presented by treatment group stratified by ApoE status.

A listing of study drug administration records, including dose level at each infusion, cumulative number of infusions and cumulative dose will be provided. A listing of aducanumab lot numbers will be provided.

A listing of study drug administration records for placebo subjects who received any doses of active treatment will be provided.

4.3 Efficacy Analysis

4.3.1 General Considerations

For efficacy endpoints, the following treatment groups of aducanumab (per randomization) will be evaluated and compared with placebo:

- Aducanumab high-dose (10 mg/kg in ApoE ε4 carriers [including 6 mg/kg for subjects enrolled under protocol versions 1-3 who do not have the opportunity to uptitrate to 10 mg/kg prior to completing Week 78 of the study] and 10 mg/kg in ApoE ε4 non-carriers).
- Aducanumab low-dose (3 mg/kg in ApoE ε4 carriers and 6 mg/kg in ApoE ε4 non-carriers).

All efficacy analyses will be performed on the ITT population. In addition, the primary and secondary endpoints will also be performed on the per-protocol population. The efficacy analysis will be presented by treatment group (per randomization), i.e., aducanumab high-dose, aducanumab low-dose and placebo (analysis display A in Appendix 6.1).

The primary, sensitivity and supplementary analyses for the primary and secondary endpoints are listed in Table 2.

Table 2. Analysis for Primary and Secondary Endpoints

Endpoint	Analysis	Analysis Population	SAP Section
CDR-SB	Primary: Analysis of change from baseline at Week 78 (MMRM)	ITT	4.3.2.1
	Sensitivity: Pattern mixture model (ANCOVA)	ITT	4.3.2.2.1
	Sensitivity: Copy increment from reference method (ANCOVA)	ITT	4.3.2.2.2
	Sensitivity: Imputation by natural disease progression (ANCOVA)	ITT	4.3.2.2.3
	Sensitivity: Tipping point analysis (ANCOVA)	ITT	4.3.2.2.4
	Supplementary: Censoring after intercurrent events (MMRM)*	ITT	4.3.2.3.1
	Supplementary: Per-protocol analysis (MMRM)	Per-protocol	4.3.2.3.2
	Supplementary: Responder analysis (Logistic regression)	ITT	4.3.2.3.3
	Supplementary: Slope analysis (MMRM)	ITT	4.3.2.3.4
	Supplementary: Divergence effect analysis (MMRM)	ITT	4.3.2.3.5
MMSE,	Primary: Analysis of change from baseline at Week 78 (MMRM)	ITT	4.3.3.1, 4.3.3.2, 4.3.3.3

ADAS-Cog 13, ADCS-ADL-MCI	Sensitivity: Pattern mixture model (ANCOVA)	ITT	4.3.3.4
	Supplementary: Censoring after intercurrent events (MMRM)*	ITT	4.3.3.4
	Supplementary: Per-protocol analysis (MMRM)	Per-protocol	4.3.3.4
	Supplementary: Slope analysis (MMRM)	ITT	4.3.3.4
	Supplementary: Divergence effect analysis (MMRM)	ITT	4.3.3.4

* Analysis excludes data collected after the following intercurrent events: (1) premature discontinuation of the study treatment and (2) any change to concomitant AD symptomatic medications during the study. All other analyses will include data collected after intercurrent events [ICH E9 (R1) Addendum 2017].

Visit windows for mapping efficacy endpoint

For efficacy data that are summarized or analyzed by visit, data collected on all scheduled visits and all unscheduled visits will be mapped to an appropriate analysis visit using the windowing scheme shown in Table 3. If there are 2 or more assessments available in the same analysis window for a subject, the assessment that is closest to the target visit day will be used for analysis. If there are 2 or more assessments in the same analysis window with the same distance from the target visit day, the later assessment will be used.

Table 3. Visit Windows for Efficacy Endpoints

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 26	183	[92, 266]
Week 50	351	[267, 448]
Week 78	547	[449, the end day of the placebo-controlled period *]
* The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter LTE, and is the last day in study for subjects who do not enter LTE.		

Handling of missing items for scales

If any of the individual items for the primary and secondary endpoints is missing, the total score of the corresponding endpoint will be imputed by prorating the observed scores [van Ginkel 2010].

For ADAS-Cog13, if 3 or fewer of 13 items (<25%) are missing, the total score will be imputed by the following algorithm: Total score = total score from the completed items * [maximum total score (=85) / maximum total score for the completed items]. The imputed number will be rounded up to the nearest integer. If more than 3 items are missing, the total score of ADAS-Cog 13 at that visit will be considered missing.

For ADCS-ADL-MCI, if 4 or fewer of 18 items (<25%) are missing, the total score will be imputed by a similar algorithm as that for ADAS-Cog 13. The imputed number will be

rounded up to the nearest integer. If more than 4 items are missing, the total score for ADCS-ADL-MCI at that visit will be considered missing.

The same imputation algorithm will be applied to CDR-SB and MMSE, if only 1 box (of 6) of CDR is missing or if only 2 or fewer items (out of 11) are missing for MMSE. If the score from more than 1 box of CDR or more than 2 items of MMSE is not available, the CDR-SB or MMSE at that visit will be considered missing.

The total score of the tertiary endpoint NPI-10 will be imputed using the same prorating principle if only 1 item (out of 10) is missing. For EQ-5D and mPDQ-20, if any item is missing, any total or sum involving that item will be considered missing.

Considerations for multiple comparison adjustments

A sequential (closed) testing procedure will be used to control the overall Type I error rate due to multiple comparisons for the primary endpoint. The order of treatment comparisons is as follows: aducanumab high-dose versus placebo and aducanumab low-dose versus placebo. All comparisons after the initial comparison with $p > 0.05$ will not be considered statistically significant.

Secondary endpoints have been rank prioritized, in the order shown in Section 1.2. In order to control for a Type I error for the secondary endpoints, a sequential closed testing procedure will be used and will include both the order of the secondary endpoints and treatment comparisons. Specifically, for each of the secondary endpoints, a sequential (closed) testing procedure, as for the primary endpoint, will be used to control the overall Type I error rate due to multiple treatment comparisons. If statistical significance is not achieved for 1 or 2 treatment comparisons, all endpoint(s) of a lower rank will not be considered statistically significant for that 1or 2 treatment comparisons, respectively.

There will be no multiple comparison adjustments for the sensitivity and supplementary analyses for the primary and secondary efficacy endpoints, the tertiary efficacy endpoints, the subgroup analyses or the additional analyses.

4.3.2 Primary Efficacy Endpoint

4.3.2.1 Primary analysis

The estimand of the primary analysis is the mean difference of the change from baseline CDR-SB scores at Week 78 between treatment groups in the ITT population [ICH E9 (R1) Addendum 2014, 2017]. All observed data will be included in the primary analysis, including data collected after intercurrent events [ICH E9 (R1) Addendum 2017], i.e., treatment discontinuation or a change in concomitant use of AD symptomatic medication.

The change from baseline CDR-SB scores will be summarized by treatment group at each post-baseline visit. A mixed model repeated measures (MMRM) model will be used as the primary analysis to analyze change from baseline CDR-SB using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline CDR-SB, baseline CDR-SB by time interaction, baseline MMSE, AD symptomatic medication use at baseline (yes/no; see Section 4.2.3 for definition of AD symptomatic medication use at baseline),

region, and laboratory ApoE ε4 status (carrier/non-carrier). An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive covariance structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. In the primary analysis, missing data are assumed to be missing at random [Rubin 1976].

4.3.2.2 Sensitivity analysis

The following sensitivity analyses will be performed to assess the robustness of the primary analysis to deviation from the missing-at-random assumption. All the sensitivity analyses will be conducted for the ITT population.

4.3.2.2.1 Pattern mixture model

The pattern mixture model (PMM) represents a general and flexible framework to model the predictive distribution of missing data conditional on the observed data [Little 1993, 1994]. It allows formulating assumptions regarding missing data in a transparent and clinically interpretable manner.

In the PMM framework, subjects are grouped into missing patterns so that subjects in the same pattern share similar missingness characteristics. In this analysis, missing patterns will be defined according to the reasons for early withdrawal from study as reported on the electronic case report form (eCRF). The following two patterns will be considered:

- Subjects who withdraw due to reasons that may be related to efficacy, including consent withdrawn, withdrawal by parent/guardian, investigator decision, loss of capacity, change of treatment, and disease progression;
- Subjects who withdraw due to reasons that are unlikely related to efficacy, including adverse event, lost to follow-up, death, pregnancy, relocation, protocol amendment, site terminated by sponsor/investigator, study visit burden, and other.

Subjects who withdraw due to reasons that may be related to efficacy will be penalized and their missing data will be imputed using the copy increment from reference (CIR) method [Carpenter et al. 2013] (see Section 4.3.2.2.2 for description of the CIR method). Subjects who withdraw due to reasons that are unlikely related to efficacy will be handled using the missing-at-random assumption and their missing data will be imputed using the standard multiple imputation method [Rubin 1987]. Subjects with missing data due to reasons other than early withdrawal (such as item missing, out of window, etc.) will be handled using the missing-at-random assumption. For both imputation methods, the following covariates will be included in the imputation model: treatment group, baseline CDR-SB, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). Implementation details can be found in Appendix 6.3.2.

The imputed datasets will be analyzed by an analysis of covariance (ANCOVA) model adjusting treatment group, baseline CDR-SB, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). The analyzed results from the imputed datasets will be combined based on Rubin's rules [Rubin

1987] assuming that the statistics estimated from each imputed dataset are normally distributed.

If intermediate missing values are encountered (such as data missing at Week 26 but are available at subsequent visits), a Markov chain Monte Carlo (MCMC) method that assumes multivariate normality will be used to impute the intermediate missing values and produce a monotone missing pattern (data with only terminal missing and no intermediate missing) [Li 1988; Schafer 1997].

4.3.2.2.2 Copy increment from reference method

The copy increment from reference (CIR) method will be applied to impute the post-withdrawal data for any aducanumab-treated subject who withdraws from study early based on data from the placebo group rather than the subject's own randomized treatment group [Carpenter et al. 2013]. Specifically, for a subject on aducanumab high dose (or aducanumab low dose) who withdraws early, his or her mean trajectory after early withdrawal is assumed to be parallel to the mean trajectory of the placebo group, and the difference between the two means is the same as the difference at the time of withdrawal. This method assumes that any benefit gained from previous treatment will be retained, but subjects progress as if they were on placebo after withdrawal from study. For any subject on placebo who withdraws early, his or her post-withdrawal profile will be imputed following the missing-at-random principle. Implementation details can be found in Appendix 6.3.1.

After all missing data have been imputed, an ANCOVA model adjusting treatment group, baseline CDR-SB, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier) will be applied to analyze the change from baseline CDR-SB.

4.3.2.2.3 Imputation by natural disease progression

Subjects are assumed to exhibit an evolution of the disease similar as the natural disease progression after early withdrawal from study (for all treatment groups). The natural disease progression is determined based on a snapshot of the Alzheimer's Disease Neuroimaging Initiative (ADNI) database [Mueller et al. 2005] obtained in May 2017. A subpopulation was defined that satisfies the major inclusion criteria of Study 221AD302 (and the identically designed Study 221AD301). In this subpopulation, the mean change from baseline CDR-SB at Week 78 is estimated to be about 1.52 for subjects with late mild cognitive impairment (LMCI) and about 2.06 for subjects with mild AD. The missing data at Week 78 for this study will be imputed using the linear extrapolation approach based on subjects' baseline clinical stage (MCI due to AD or mild AD). For example, assuming a mild AD patient whose last non-missing change from baseline CDR-SB measurement is 0.5 at Week 26, the change from baseline CDR-SB at Week 78 for this patient will be imputed as 0.5+2.06*(78-26)/78, which is 1.87. A similar algorithm will be applied to the MCI patients. After imputation, the change from baseline CDR-SB at Week 78 will be analyzed by an ANCOVA model adjusting treatment group, baseline CDR-SB, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier).

4.3.2.2.4 Tipping point analysis

The tipping-point analysis is a progressive stress-testing to assess how severe departures from missing-at-random must be in order to overturn the conclusion of the primary analysis [Yan et al. 2009]. For our study, subjects are assumed to have worse scores after early withdrawal from study compared to subjects who remain on study.

The missing data are first imputed by the standard multiple imputation (assuming missing at random). To reflect the worse performance after early withdrawal, pre-specified shift parameters δ_c and δ_t are added to the imputed values for subjects on placebo and aducanumab (include both low dose and high dose), respectively. The adjusted multiple imputed datasets will then be analyzed by an ANCOVA model and the results will be combined using the Rubin's rule for inference.

A range of shift parameters δ_c and δ_t will be applied and p-value will be calculated for each combination of δ_c and δ_t. The tipping region is defined as the combinations of δ_c and δ_t such that the treatment effect is no longer significant (p-value greater than the significance level).

The scientific plausibility of the tipping region will be evaluated. If implausible departures from the missing-at-random assumption (large δ) are needed in order to change the results from statistically significant to insignificant, the results of the primary analysis are considered to be robust to departure from the missing-at-random assumption.

4.3.2.3 Supplementary analysis

4.3.2.3.1 Censoring after intercurrent events

The primary analysis (Section 4.3.2.1) will be repeated with the data censored after any of the following intercurrent events (if multiple events occur to the same subject, data after the earliest event will be censored):

- premature discontinuation of the study treatment;
- any change to concomitant AD symptomatic medications during the study.

The estimate of this analysis reflects the treatment effect of aducanumab if the drug is taken as directed.

4.3.2.3.2 Per-protocol analysis

The per-protocol analysis will be done using the same model as the primary analysis (Section 4.3.2.1) and applying in the per-protocol population (Section 4.1.1).

4.3.2.3.3 Responder analysis

To further assess whether subjects on aducanumab progress differently from those on placebo, responder analysis will be conducted. The responders will be determined by a threshold of the primary endpoint, i.e., subjects whose change from baseline CDR-SB at Week 78 is smaller than or equal to the threshold will be classified as responders and otherwise will be classified as non-responders. All subjects with missing data at Week 78 will be classified as non-responders.

The responder analysis will be conducted for two threshold values: 0.5 or 1.5, i.e., subjects whose change from baseline CDR-SB at Week 78 ≤ 0.5 or ≤ 1.5. The number of responders

and the response rate will be summarized by treatment group. The dichotomized response, responder vs. non-responder, will be modeled using a logistic regression with the following covariates: treatment group, baseline CDR-SB, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratoy ApoE ε4 status (carrier/non-carrier). In addition to the two selected threshold values, the continuous responder curve that displays the percentage of responders under a wide range of threshold values will be presented by treatment group.

Since all missing data will be considered as non-response, which is a special form of missing-not-at-random, this analysis can provide additional insights for the robustness of the primary analysis results.

4.3.2.3.4 Slope analysis

Slope analysis will be conducted to assess the difference between each aducanumab treatment group and placebo in the slope of change from baseline in CDR-SB up to Week 78. A reduction in the slope of the aducanumab treatment group compared with placebo would indicate a slower rate of disease progression, thus reflecting a disease modifying effect of aducanumab. An MMRM model will be used, with dependent variable as the change from baseline CDR-SB score at each visit and with fixed effects of treatment group, time (as a continuous variable), treatment group-by-time interaction, baseline CDR-SB, baseline CDR-SB by time, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). The continuous time variable is calculated as number of years since the 1st infusion, so the slope estimate reflects the annual rate of change. The same methods as in the primary analysis will be considered for the covariance structure and the degrees of freedom.

4.3.2.3.5 Divergence effect analysis

A divergence effect analysis will be performed to assess whether the treatment difference between the aducanumab treated patients and the placebo patients increases over time [Li 2017]. A linear trend test will be conducted on treatment difference at Week 26, 50 and 78 estimated from the MMRM model of Section 4.3.2.1, to assess if the slope of the treatment difference is positive or not. Let the estimate of treatment difference be δ_i at time point t_i, where $t_i = 26$, 50 and 78 (week). The least-square estimate of the slope is

$$\beta_{DIF} = \frac{\sum(t_i - \bar{t})\delta_i}{\sum(t_i - \bar{t})^2},$$

where $\bar{t}$ is the mean of t_i's. The hypothesis to be tested is

$$H_0: \beta_{DIF} \leq 0 \quad \text{versus} \quad H_a: \beta_{DIF} > 0.$$

Given β_{DIF} is a linear combination of the treatment difference δ_i, this analysis can be implemented by the "estimate" statement in the SAS proc mixed procedure.

4.3.2.4 CDR subscores and CDR global score

The CDR is comprised of 6 domains: Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. CDR-SB is the sum of the scores

for these 6 domains. In addition, two CDR subscores have been proposed [Tractenberg 2005]: a "cognitive" subscore equaling the sum of the Memory, Orientation, and Judgment and Problem Solving box scores, and a "functional" subscore equaling the sum of Community Affairs, Home and Hobbies and Personal Care box scores. For each of the 6 box scores, and the CDR cognitive subscore and CDR functional subscore, the baseline value and the change from baseline at each post-baseline visit will be summarized by treatment group. The same MMRM model as the primary analysis will also be applied to the CDR cognitive subscore and CDR functional subscore.

The CDR global score is a composite score obtained by combining the 6 box scores using a scoring algorithm that weights memory as the primary domain and all other domains as secondary [Morris 1993]. The distribution of CDR global score will be summarized (as a categorical variable) by treatment group at each post-baseline visit.

4.3.3 Secondary Efficacy Endpoints

4.3.3.1 Primary analysis of MMSE

The change from baseline MMSE scores will be summarized by treatment group at each post-baseline visit. An MMRM model will be used as the primary analysis to analyze change from baseline MMSE using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline MMSE value, baseline MMSE by time interaction, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). The same methods as in the primary analysis will be considered for the covariance structure and the degrees of freedom.

4.3.3.2 Primary analysis of ADAS-Cog 13

The change from baseline ADAS-Cog 13 scores will be summarized by treatment group at each post-baseline visit. An MMRM model will be used as the primary analysis to analyze change from baseline ADAS-Cog 13 using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline ADAS-Cog 13, baseline ADAS-Cog 13 by time interaction, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). The same methods as in the primary analysis will be considered for the covariance structure and the degrees of freedom.

4.3.3.3 Primary analysis of ADCS-ADL-MCI

The change from baseline ADCS-ADL-MCI scores will be summarized by treatment group at each post-baseline visit. An MMRM model will be used as the primary analysis to analyze change from baseline ADCS-ADL-MCI using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline ADCS-ADL-MCI, baseline ADCS-ADL-MCI by time interaction, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). The same methods as in the primary analysis will be considered for the covariance structure and the degrees of freedom.

The primary analysis of ADCS-ADL-MCI will use the pooled data from both Studies 221AD301 and 221AD302 (analysis for each individual study will also be performed). Pooled data will be used for the primary analysis because functional outcomes are expected to be less sensitive to change within the study duration than cognition measures due to ceiling effects [Rockwood 2007], as subjects entering the study will have no or little measurable impairment at baseline. It has also been observed in previous studies of more impaired patients (mild to moderate/severe) that functional outcome treatment effect sizes are small [Hansen 2007].

4.3.3.4 Sensitivity/Supplementary analysis

The following sensitivity and supplementary analyses that are planned for the primary efficacy endpoint will also be conducted for the secondary efficacy endpoints:

- Pattern mixture model
- Censoring after intercurrent events
- Per-protocol analysis
- Slope analysis
- Divergence effect analysis

4.3.4 Tertiary Endpoints for Efficacy and Quality of Life

The baseline value and the change from baseline at each post-baseline visit for NPI-10 will be summarized by treatment group. An MMRM model will be used to analyze the change from baseline in NPI-10 using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline NPI-10, baseline NPI-10 by time interaction, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). Same methods as in the primary analysis will be considered for the covariance structure and the degrees of freedom.

For the following tertiary endpoints for patient-reported outcomes and quality of life, subject self-reported EQ-5D index score (SR), informant-rated subject EQ-5D index score (IR-S), and mPDQ-20, the baseline value and the change from baseline at each post-baseline visit will be summarized by treatment group. Additional analyses for these endpoints will be provided in a separate document.

4.3.5 Subgroup Analysis

Subgroup analyses will be performed for the primary endpoint (CDR-SB) and secondary endpoints (MMSE, ADAS-Cog13, ADAS-ADL-MCI). The following pre-defined subgroups will be considered:

- Laboratory ApoE ε4 status (carrier or non-carrier)
- Baseline clinical stage (MCI due to AD or mild AD) per the Investigator's assessment based on the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria
- Use of AD symptomatic medication at baseline (yes or no)

- Baseline MMSE (MMSE ≤ 26 or MMSE ≥ 27)
- Region (US, Europe/Canada/Australia, Asia; see Section 4.2.1 for definition of region)
- Age category (≤ 64, 65-74, ≥ 75)
- Gender (female or male)

A selective set of subgroup analyses will be performed for Amyloid PET data. Details will be defined in Sections 4.4.

4.4 Amyloid PET Analysis

4.4.1 Amyloid PET substudy

Every subject enrolled into the study must have a positive amyloid PET scan by visual read either at screening or obtained within 12 months of screening. Subjects enrolled into the amyloid PET substudy will have the quantitative standard uptake value ratio (SUVR) scores at screening and at each planned post-baseline visit. The amyloid PET substudy will include a subset of approximately 400 subjects in countries other than Japan where PET scans will be performed using ^{18}F-florbetapir ligand, and a small subset of subjects in Japan where either ^{18}F-florbetapir ligand or ^{18}F-flutemetamol ligand will be used. In the placebo-controlled period, amyloid PET assessments are scheduled at screening, Week 26, and Week 78.

4.4.2 Amyloid PET SUVR regions-of-interest and reference regions

Amyloid PET standardized uptake value ratio (SUVR) is a quantitative measure of cerebral amyloid plaque burden. The SUVR will be calculated for the following target brain regions-of-interest (ROIs): composite ROI, frontal cortex, parietal cortex, lateral temporal cortex, sensorimotor cortex, anterior cingulate cortex, posterior cingulate cortex, medial temporal cortex, occipital cortex, striatum, and statistical ROI normalized to reference region activity. Additionally, SUVR ROIs including pons and deep subcortical white matter which are believed to be least affected by amyloid pathology will also be evaluated. The composite ROI will comprise of major cortical regions part of the frontal, parietal, lateral temporal, sensorimotor, anterior, posterior cingulate and occipital cortices to serve as a summary measure of global cerebral amyloid burden. The statistical ROI is a region of interest consisting of the posterior cingulate cortex, precuneus and medial frontal cortex that has been demonstrated to yield optimal group separation between subjects with low and high amyloid burden across different reference regions. A negative change from baseline in composite ROI SUVR indicates a reduction in amyloid burden and a negative treatment difference (aducanumab minus placebo) favors aducanumab. The composite ROI will serve as the ROI of primary focus.

The following reference regions will be employed: cerebellum, cerebellum cropped, cerebellar white matter, cerebellar grey matter, deep subcortical white matter, pons, cerebellum + pons, cerebellar white matter + pons, deep subcortical white matter + cerebellum, deep subcortical white matter + pons and deep subcortical white matter + cerebellum + pons. Cerebellum will serve as the reference region of primary focus.

The composite ROI SUVR using cerebellum as the reference region will be used as the primary endpoint for amyloid PET analysis.

4.4.3 Amyloid PET analysis population

There are two amyloid PET analysis population: ^{18}F-florbetapir amyloid PET analysis population and ^{18}F-flutemetamol amyloid PET analysis population.

The following background characteristics tables will be generated for the ^{18}F-florbetapir amyloid PET analysis population and will be presented by treatment group: number of subjects enrolled by region and country, demography, baseline disease characteristics, medical history. The content of these tables will be the same as those described in section 4.2 for the ITT population, with the addition of baseline amyloid PET SUVR values summarized for the baseline characteristics of AD.

4.4.4 By visit summary and MMRM model

The baseline and change from baseline amyloid PET SUVR values will be summarized by treatment groups (placebo, low dose and high dose) and by visit for each of the target ROIs using cerebellum as the reference region for each of the amyloid PET analysis populations. In addition, the baseline and change from baseline amyloid composite ROI values will be summarized by treatment groups by visit for each of the reference regions for each of the amyloid PET analysis populations.

For the ^{18}F-florbetapir amyloid PET analysis population, an MMRM model will be used to analyze change from baseline SUVR for each target ROI with cerebellum as the reference region. Fixed effects of the model will include treatment groups (placebo, low dose and high dose), visit (Week 26 and Week 78), treatment group-by-visit interaction, baseline SUVR (continuous), baseline SUVR by visit interaction, baseline MMSE (continuous), laboratory ApoE ε4 status (carrier and non-carrier), and baseline age (continuous). Visit and treatment group will be treated as categorical variables in the model along with their interactions. An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence in any of the parameters, the heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive covariance structure will be used for all the parameters. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Adjusted means for each treatment group, pairwise adjusted differences with placebo, 95% confidence intervals for the differences and associated p-values will be presented at week 26 and week 78. The same MMRM model will also be used to analyze the change from baseline SUVR for the composite ROI with each of the reference regions. No multiple comparison adjustment will be used for amyloid PET analysis.

Subgroup analysis will be conducted on the ^{18}F-florbetapir amyloid PET analysis population using the same MMRM model for composite ROI using cerebellum as reference region for the following stratification factors: laboratory ApoE status (carrier or non-carrier, and this model will not use ApoE status as a covariate), baseline clinical stage (MCI due to AD or mild AD) and baseline composite ROI SUVR value in quartiles.

Visit windows for by visit analysis

For amyloid PET by visit summaries and MMRM models, the analysis visit should be defined using visit windows (see Table 4 below). The rationale is to use the same analysis visit windows as for the efficacy endpoints for Week 26 and Week 78. If there is more than 1 value in the same analysis visit window (>1 value for the same analysis visit) for a certain parameter for a subject, then the closest record to the target visit day will be used for the by visit analysis. If they are with the same distance from the target visit day, then the record with the later time will be used for the by visit analysis.

Table 4: Visit Windows for amyloid PET data

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 26	183	[92, 266]
Week 78	547	[449, the end day of the placebo-controlled period**]
* The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter in LTE, and is the last day in study for subjects who do not enter LTE.		

4.4.5 Correlation between amyloid PET and CDR sum of boxes

Pearson and Spearman correlation

Pearson and Spearman correlations between change from baseline amyloid PET composite ROI using cerebellum as reference region at Week 78 and change from baseline CDR-SB at Week 78 will be conducted by treatment groups (placebo, low dose and high dose, and active total) in the ^{18}F-florbetapir amyloid PET analysis population. Pearson and Spearman partial correlations adjusting for baseline amyloid PET composite ROI and baseline CDR-SB will also be conducted by treatment groups at Week 78. The estimated correlation coefficients, p-values and the 95% confidence intervals will be provided. Given that reductions in cerebral β-amyloid (Aβ) content may precede clinical effects (e.g., slowing of clinical decline), Pearson and Spearman correlations and partial correlations between change from baseline amyloid PET composite ROI at Week 26 and change from baseline CDR-SB at Week 78 will also be conducted.

Correlation analysis will be done on each individual study as well as in the pooled data of the 221AD301 and 221AD302 studies. The correlation analysis based on the pooled data will be considered as the primary analysis.

4.5 Safety Analysis

4.5.1 General Considerations

Analysis population

Safety population will be used for safety analyses of AEs, clinical laboratory data, Columbia Suicide Severity Rating Scale (C-SSRS) data, ECG data and vital sign data (all the safety data except for ARIA data). Safety MRI population will be used for analyses of ARIA data.

Safety treatment groups

Different from the randomization treatment groups, if a subject who was randomized to placebo group accidentally received one or more doses of the active treatment during the study, he/she will be classified as either low or high dose group for all the safety analyses, depending on the ApoE status and the maximal dose level of the active treatment received (Table 5). A listing of such subjects will be provided, as described in section 4.2.5. Safety treatment groups will be the same as the randomization treatment groups for other subjects (subjects randomized to active treatment groups, and subjects randomized to placebo without any accidental active dose). Safety treatment groups will be used for all the safety analyses unless otherwise specified.

Table 5: Safety treatment groups for placebo subjects with accidental active treatment

Randomization treatment group	Randomization ApoE status	Safety treatment group classification based on the maximum dose level of the accidental active treatment		
		>0 to 3 mg/kg	>3 to 6 mg/kg	>6 mg/kg
Placebo	ApoE ε4 (+)	Low dose	High dose	High dose
	ApoE ε4 (-)	Low dose	Low dose	High dose

Safety analysis displays

AEs, clinical laboratory data, C-SSRS data, ECG data and vital sign data (all the safety data except for ARIA data) will be summarized by treatment group (placebo, low dose, high dose and BIIB037 total; analysis display A in Appendix 6.1), unless otherwise specified. All the ARIA related tables will be presented by treatment group stratified by ApoE status (3 columns under each treatment group: ApoE ε4+, ApoE ε4- and total; analysis display B in Appendix 6.1), unless otherwise specified. A subset of AE tables will also be presented by treatment group stratified by ApoE status in addition to by treatment group. All the listings will be presented by treatment group stratified by ApoE status.

Incidence, incidence proportion and incidence rate

- Incidence and incidence proportion will be provided in incidence tables. Incidence is defined as the number of subjects who experienced an event. Incidence proportion is defined as the number of subjects who experienced an event divided by total number of subjects in the analysis population, i.e., percentage. Each subject will be counted only once within each category.

- Incidence and incidence rate will be provided in incidence rate tables. Two different kinds of incidence rate tables will be provided as appropriate for different analyses. Definitions are provided below.

  (1) Follow-up adjusted incidence rate – defined as the number of subjects who experienced an event divided by the total of entire follow-up time among the subjects in the analysis population. The entire follow-up time for a subject is defined as the time from the first dose until the last day on study. Each subject will be counted only once within each category.
  (2) Exposure-adjusted incidence rate (EAIR) – defined as the number of subjects who experience an event divided by the total exposure adjusted follow-up time among the subjects in the analysis population. The exposure adjusted follow-up time is defined as the time from the first dose until the initial occurrence of the event for those who experienced an event, or from the first dose until the end of follow-up (the last day on study) for those who did not. Each subject will be counted only once within each category.

4.5.2 Clinical Adverse Events

Treatment-emergent AEs (TEAEs)

All AEs will be analyzed based on the principle of treatment emergence. A treatment-emergent AE was defined as an AE that started or worsened after the start of first infusion of study treatment.

To define treatment emergence for AEs with missing start or stop date or time the following additional criteria will be used:

- if both the start and stop dates for a particular AE are missing, then that AE is considered treatment emergent;
- if the start date for a particular AE is missing and the stop date/time falls after the first dose date/time, then that AE is considered treatment emergent;
- if the start date for a particular AE was the same as the first dose date, and the start time was missing, then that event is considered treatment emergent.

For AEs with a partial start date, the year/month of the event date will be compared to that of the first dosing date to determine whether the event is treatment emergent.

In addition, SAEs that occurred since a subject was screened in the study and prior to the first infusion of study treatment, which by definition are not treatment-emergent, will be analyzed separately.

Only TEAEs will be included in the AE tables, unless otherwise specified. Listings of AEs will include all events, whether treatment-emergent or not.

As specified in the protocol, subjects were expected to return to the study site for an End of Study visit 18 weeks after the last administration of study treatment. However, some subjects may elect to continue study participation on a modified schedule after discontinuing treatment, possibly in substantial excess of 18 weeks. For most general AE summaries, AEs

with an onset more than 18 weeks after the last dose will be excluded (will specify in the footnote of the specific table). For incidence rate analyses excluding AEs more than 18 weeks after the last dose, the "last day on study" in follow-up time calculation will be replaced with "18 weeks after last dose or last day on study, whichever earlier". Summaries of deaths and AEs leading to study withdrawal, and other selected analyses will include all AEs regardless of the time since the last dose. Listings will include all AEs, unless otherwise specified.

4.5.2.1 Summary and incidence analysis

Overall summary of AE table will summarize the number of subjects with any AE, with any AE by maximum severity, the number of subjects with any related AE (related to study drug as assessed by investigator), the number of subjects with SAE, the number of subjects with related SAE, the number of subjects with AE leading to study drug discontinuation, the number of subjects with AE leading to study withdrawal, and the number of deaths. This table will be done by treatment group as well as by treatment group stratified by ApoE status.

The sorting order for AE incidence tables, unless otherwise specified, will be by decreasing frequency order of "BIIB037 total" column within each category in the tables presented by treatment group, and by decreasing frequency order of "BIIB037 high dose total" column within each category in the tables presented by treatment group stratified by ApoE status. A subject is counted only once within each category in each table. For example, for the table of AEs by system organ class and preferred terms sorted by decreasing frequency presented by treatment group, system organ class will be presented in decreasing frequency order of BIIB037 total column, and within each system organ class, preferred terms will be presented in decreasing frequency order of BIIB037 total column. A subject is counted only once within each system organ class and preferred term.

The following AE incidence tables will be provided (presented both by treatment group and by treatment group stratified by ApoE status, unless otherwise specified):

1. AEs by system organ class and preferred term sorted by decreasing frequency
2. AEs by system organ class and preferred term sorted by alphabetical order (by treatment group)
3. AEs by system organ class, high level group term and preferred term (by treatment group only)
4. AEs by system organ class (by treatment group)
5. AEs with at least 2% higher in incidence for either low or high dose compared to placebo by system organ class and preferred term
6. AEs by preferred term
7. AEs with an incidence of 5% or more in any treatment group by preferred term
8. Severe AEs by system organ class and preferred term (by treatment group)
9. Severe AEs by preferred term
10. AEs by maximum severity by system organ class and preferred term (by treatment group) (System organ class will be presented alphabetically. Preferred terms will be presented in decreasing frequency order. Maximum severity will be presented within each preferred term in the order of mild, moderate, severe, unknown and total. A

subject will be counted only once at the maximum severity within each system organ class and preferred term.)

11. AEs by maximum severity by preferred term (by treatment group) (Preferred terms will be presented in decreasing frequency order. Maximum severity will be presented within each preferred term in the order of mild, moderate, severe, unknown and total. A subject will be counted only once at the maximum severity within each preferred term.)
12. Related AEs by system organ class and preferred term
13. SAEs by system organ class and preferred term
14. SAEs by preferred term
15. Related SAEs by system organ class and preferred term
16. AEs that led to discontinuation of study treatment by system organ class and preferred term
17. AEs that led to withdrawal from study by system organ class and preferred term
18. SAEs with fatal outcome by system organ class and preferred term
19. AEs that occurred within 2 hours from infusion start by system organ class and preferred term (by treatment group)
20. AEs by12 weeks intervals from first infusion to the end of study by system organ class and preferred term (by treatment group)
21. Pre-treatment SAEs that occurred since screening and prior to first infusion by system organ class and preferred term

The following listings will be provided.

1. Listing of AEs
2. Listing of SAEs
3. Listing of AEs that led to discontinuation of study treatment
4. Listing of AEs that led to withdrawal from study
5. Listing of AEs that occurred within 2 hours from infusion start
6. Listing of AEs related to PET ligands
7. Listing of SAEs with fatal outcome
8. Listing of AEs for subjects with treatment-emergent positive anti-BIIB037 antibody

4.5.2.2 Incidence rate analysis

Follow-up adjusted incidence rate for the placebo-controlled period will be summarized by system organ class and preferred terms both by treatment group and by treatment group stratified by ApoE status.

4.5.2.3 Subgroup analysis for protocol version 4

Due to the change in maximal dose from 6 mg/kg to 10 mg/kg for ApoE ε4 carrier high dose group in protocol version 4, not all subjects have had opportunity to receive the protocol specified high dose (6 doses in titration before receive 10mg/kg) in the placebo-controlled period. Incidence tables of AEs and SAEs will be provided for ApoE ε4 carriers who were randomized to the high dose group, stratified by the expected number of doses at 10 mg/kg (categories of 0, 1-6, 7-13, 14, and a total column of having at least one dose) a subject would have received based on the first infusion date and the date consenting to protocol version 4. Randomization treatment groups will be used for this analysis.

4.5.3 ARIA – AE of special interest

4.5.3.1 Background

ARIA is an AE of special interest in this study. Please see protocol section 7.2.1 for ARIA management and dose disposition guidelines. Since ARIA is a brain MRI finding, ARIA data are collected under two data sources: (1) safety MRI data as recorded on brain MRI worksheet by central MRI reader; (2) AE eCRF. For each ARIA event, the information of start/end date, severity, locations in brain regions and status on MRI scan is collected on the brain MRI worksheet by central MRI reader. ARIA severity is determined by central MRI reader based on number and size of the ARIA regions on imaging. An AE record is then entered into the eCRF by the investigator with the start/end date and severity information from brain MRI worksheet, and with information on the symptomatic status and action taken towards study drug. If ARIA is symptomatic, the symptoms will be entered into AE eCRF and the severity of the symptoms will be determined by the investigator. AE eCRF data will be used as the primary source for ARIA analysis as it contains the complete information of ARIA as well as associated symptoms. Safety MRI data will also be used to show the consistency between two data sources, provide details on MRI assessments, and for any specific analysis that requires information from MRI.

ARIA includes ARIA-E (vasogenic edema) and ARIA-H (hemorrhage). ARIA-H includes ARIA-H microhemorrhage, ARIA-H macrohemorrhage and ARIA-H superficial siderosis. Table 6 shows the reported term on MRI worksheet, the corresponding reported term on AE eCRF, and the MedDRA preferred term and lower level term for each type of ARIA.

Table 6: Reported and MedDRA terms for ARIA

Reported term on MRI worksheet	Reported term on AE eCRF	MedDRA version 21.0 preferred term	MedDRA version 21.0 lower level term
ARIA-E	Asymptomatic ARIA-E Symptomatic ARIA-E	Amyloid related imaging abnormality-oedema/effusion	ARIA-E

ARIA-H microhemorrhage	Asymptomatic ARIA-H (Microhemorrhage) Symptomatic ARIA-H (Microhemorrhage)	Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	ARIA-H
ARIA-H macrohemorrhage	Asymptomatic ARIA-H (Macrohemorrhage) Symptomatic ARIA-H (Macrohemorrhage)	Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	ARIA-H
ARIA-H superficial siderosis	Asymptomatic ARIA-H (Superficial Siderosis) Symptomatic ARIA-H (Superficial Siderosis)	superficial siderosis of the central nervous system	superficial siderosis of the central nervous system

For any specific ARIA event, the start date of the duration based on MRI is the date of the MRI assessment that initially identifies the ARIA event, and the end date of the duration based on MRI is the date of the MRI assessment that shows the complete resolution of this ARIA event (in the case of ARIA-E), or the date of the MRI assessment that shows ARIA being stable (in the case of ARIA-H). Stable was defined as 'No change' or 'decrease' in number, size, severity or number of locations between 2 consecutive MRIs including the initial detection MRI and the follow-up MRIs.

For symptomatic ARIA events, if there is any related symptom that proceeds the first MRI identification, then the symptom onset date will be used as the start date of the symptomatic ARIA duration. The end date of the symptomatic ARIA duration will be the date of the resolution or stable MRI as defined above for the duration based on MRI.

If the severity increases, or the event changes from asymptomatic to symptomatic, or from non-serious to serious, more than one AE records will be added to eCRF to capture the change with new start/end AE dates (the end date of the previous record will be the start date of the next record). For analysis, records with changes in severity or symptomatic status or seriousness are considered as a single ARIA event. The severity/symptomatic status/seriousness for that event is defined as the worst level among all the AE records that belong to that event.

If the same type of ARIA event happens again after the previous event has ended, then it is considered a recurrent event of ARIA of that type. Recurrent events will be referred as the second event, the third event, and etc.

If the duration based on MRI of an ARIA-E event overlaps with the duration based on MRI of an ARIA-H event, then these 2 ARIA events are considered as concurrent events.

4.5.3.2 Incidence and summary of ARIA

Incidence of ARIA-E, ARIA-H, ARIA-E and ARIA-H (not necessarily concurrent), concurrent ARIA-E and ARIA-H, ARIA-E or ARIA-H, isolated ARIA-H (only ARIA-H, no ARIA-E), ARIA-H microhemorrhage, ARIA-H macrohemorrhage and ARIA-H superficial siderosis will be summarized based on both AE eCRF and MRI data. If there is any discrepancy in incidence between the two data sources, a listing of the subjects and ARIA events with discrepancy will be provided. In addition, the incidence table based on AE eCRF source will also be done by treatment group (placebo, low dose, high dose and BIIB037 total; analysis display A in Appendix 6.1).

Number of subjects with each type of ARIA, maximum severity and worst symptomatic status of the type of ARIA being analyzed will be summarized based on AE eCRF. For subjects with symptomatic ARIA, the maximum severity of symptoms will also be summarized.

Number of subjects with ARIA-H microhemorrhage events post-baseline (broken down by categories of 1-4, 5-9 and >=10) stratified by whether they have had microhemorrhage at baseline will be summarized based on safety MRI data. The summary will be conducted based on the MRI that shows the maximum number of microhemorrhages as well as the last MRI in the study period.

Summary of concurrent ARIA-E and ARIA-H will be provided including the following information: number of subjects with concurrent ARIA-E and ARIA-H (and further broken down to each type of ARIA-H), the severity of ARIA-E based on MRI, the symptomatic status of ARIA-E, the severity of symptoms based on AE eCRF. For subjects with recurrent ARIA-E events, if there is an event concurrent with ARIA-H, it will be used for the summary, and the first concurrent event will be used if there are more than one event concurrent with ARIA-H.

An incidence table of AEs considered by the investigator to be related to ARIA by system organ class and preferred term for subjects with symptomatic ARIA will be provided, as well as a listing of these AEs. Similarly, an incidence table of AEs related to ARIA for subjects with symptomatic ARIA and severe symptoms will be provided, as well as a listing of these AEs.

Listings of AE records for each type of ARIA events and listings of MRI assessments for subjects with each type of ARIA events will be provided.

Montreal Cognitive Assessment (MOCA) is performed at baseline and at each unscheduled ARIA monitoring visit for ARIA subjects (approximately every 4 weeks) except for mild asymptomatic microhemorrhage subjects. An incidence table of subjects with ARIA events whose MOCA total scores decrease 2 points or more from baseline will be provided. A listing of MRI assessments and MOCA total scores for subjects with ARIA events will be provided.

Line plots of MMSE mean change from baseline values and standard errors at each planned visit (baseline, Week 26, Week 50 and Week 78) will be provided by treatment group stratified by ApoE status and with stratification on the following factors:

(1) ARIA-E severity based on MRI. The groups are: subjects without ARIA-E, subjects with mild ARIA-E, subjects with moderate ARIA-E and subjects with severe ARIA-E.

(2) Within ARIA-E subjects, stratify by the severity of the concurrent symptoms based on AE eCRF. The groups are: subjects without symptoms, subjects with mild symptoms, subjects with moderate symptoms, and subjects with severe symptoms.

For subjects with recurrent ARIA-E events, the first ARIA-E event will be used for the classification for each of the factors.

4.5.3.3 Summary of recurrent ARIA-E

Follow-up adjusted incidence rate of subjects with ARIA-E, with 2 or more events of ARIA-E, with 3 or more events of ARIA-E and with more than 3 events of ARIA-E based on their entire follow-up time will be summarized based on AE eCRF. The entire follow-up time is from the first dose until the last day in the placebo-controlled period.

Number of total ARIA-E events and the MRI severity of each event will be summarized based on AE eCRF. Number of total symptomatic ARIA-E events, the MRI severity of each symptomatic event and the severity of the symptoms of each symptomatic event will be summarized based on AE eCRF.

Summary of first ARIA-E events table based on AE eCRF will summarize the number of subjects with a first event of ARIA-E, the MRI severity of the events, the symptomatic status of the events, the severity of the symptoms for symptomatic events, whether SAE or not, number of resolved and unresolved events, duration of the resolved events, time from first infusion in study (active or placebo) to onset, number of doses received since the start of the study to onset, dose level of the last infusion received prior to onset, dosing status (continue as planned, dose interrupted, dose reduced, or dose discontinued) after the events, and the number of subjects with recurrent ARIA-E events. The same summary of first ARIA-E events table will also be done on subjects who had recurrent ARIA-E events.

Summary of recurrent ARIA-E events table based on AE eCRF will summarize the following information for both the second and third event of ARIA-E events: the number of subjects with the previous event of ARIA-E, the number of subjects with at least one dose and one MRI after the previous ARIA-E resolution, the number of subjects with this event of ARIA-E, the MRI severity of the events, the symptomatic status of the events, the severity of the symptoms for symptomatic events, whether SAE or not, number of resolved and unresolved events, duration of the resolved events, time from first infusion in study (active or placebo) to onset, time from previous resolution to onset, number of doses received since the start of the study to onset, dose level of the last infusion received prior to onset, dosing status (continue as planned, dose interrupted, dose reduced, or dose discontinued) after the events. The number of subjects with more than 3 events of ARIA-E, and the number of subjects who discontinued study treatment after recurrent ARIA-E onset will also be summarized.

A listing of subjects who withdrew from the study with unresolved ARIA-E or subjects with ongoing ARIA-E at the time of data cutoff (also considered as unresolved) will be provided with the details of the event including the duration from onset to last follow-up.

For subjects with recurrent ARIA-E, a listing of study drug administration, MRI assessments, severity and symptomatic status of each event, and end-of-treatment reason (if present) will be provided.

4.5.3.4 Exposure adjusted analysis

Exposure adjusted incidence rate of ARIA-E events will be summarized based on safety MRI data. The exposure adjusted follow-up time is from the first dose until the initial occurrence of ARIA-E for those who experienced ARIA-E, and until the end of follow-up for those who did not. Since ARIA is an MRI finding, the day of the last MRI assessment in the placebo-controlled period will be used as the end of follow-up for those who didn't experience the event.

Study drug administration information prior to first ARIA-E onset will be summarized for ARIA-E subjects, including number of total infusions, number of infusions at each dose level (placebo, 1 mg/kg, 3 mg/kg, 6 mg/kg and 10 mg/kg), dose level of the last infusion, maximum dose level received, and cumulative dose as a continuous variable.

4.5.3.5 Time to event analysis

Kaplan-Meier plot of time to first ARIA-E event will be produced based on safety MRI data. Time to event is calculated as date of the MRI assessment that initially detects ARIA-E event - date of first infusion (aducanumab or placebo) +1. Censor time for subjects without ARIA-E is calculated as date of last MRI assessment in the placebo-controlled period - date of first infusion (aducanumab or placebo) +1. Estimated proportion with ARIA-E and number of subjects at risk at selected timepoints will also be presented. The plot will be presented by treatment group stratified by ApoE status.

4.5.3.6 Subgroup analysis for protocol version 4

Due to the change in maximal dose from 6 mg/kg to 10 mg/kg for ApoE ε4 carrier high dose group in protocol version 4, not all subjects have had opportunity to receive the protocol specified high dose (6 doses in titration before receive 10mg/kg) in the placebo-controlled period. Incidence of ARIA events and summary of first ARIA-E events tables will be provided for ApoE ε4 carriers who were randomized to the high dose group, stratified by the expected number of doses at 10 mg/kg (categories of 0, 1-6, 7-13, 14, and a total column of having at least one dose) a subject would have received based on the first infusion date and the date consenting to protocol version 4. Randomization treatment groups will be used for this analysis.

4.5.4 Clinical Laboratory Data

The following clinical laboratory parameters are assessed in the protocol and will be analyzed:

- Hematology:
  - White blood cells (leukocytes), lymphocytes, neutrophils, monocytes, eosinophils, basophils
  - Red blood cells (erythrocytes), erythrocytes distribution width, erythrocytes mean corpuscular volume, erythrocytes mean corpuscular hemoglobin, erythrocytes mean corpuscular hemoglobin concentration

- Hemoglobin
- Hematocrit
- Platelet count

- Blood chemistry:
  - Liver: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, gamma-glutamyl-transferase (GGT)
  - Renal: blood urea nitrogen (BUN), creatinine
  - Electrolytes: sodium, potassium, chloride, bicarbonate
  - Other: glucose, calcium, phosphorus, albumin, uric acid, lactate dehydrogenase (LDH), total protein
- Urinalysis: specific gravity, potential of hydrogen (pH), color, blood, glucose, ketones, protein, white blood cells, red blood cells

4.5.4.1 Quantitative analyses

For numeric laboratory parameters, actual values, change from baseline and percent change from baseline will be summarized by visit. Number of evaluable subjects, mean, standard deviation, median, 25% and 75% quartiles, minimum and maximum values will be presented at each visit.

Plots of mean values (with standard error) for numeric laboratory parameters at each visit will be provided.

Listings of individual laboratory measurements by patients for all the parameters will be provided.

Visit windows for by visit summaries

For laboratory by visit summaries, the analysis visit should be defined using visit windows (see Table 7 below). If there is more than 1 value in the same analysis visit window for a certain parameter for a subject, then the closest record to the target visit day will be used for the by visit analysis. If there are 2 values in the same analysis visit window with the same distance from the target visit day for a certain parameter for a subject, then the record with the later date will be used for the by visit analysis. If there are 2 values on the same day for a certain parameter for a subject, then the record with the later time will be used for the by visit analysis.

Table 7: Visit Windows for Laboratory by Visit Summaries

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 24	169	[2, 252]
Week 48	337	[253, 420]
Week 72	505	[421, 525]

Analysis visit	Target visit day	Analysis visit window
Week 78	547	[526, the end day of the placebo-controlled period*]
* The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter LTE, and is the last day in study for subjects who do not enter LTE.		

4.5.4.2 Qualitative analyses

For all qualitative analyses, all values will be included (not just the "analyzed record" within each visit window in the quantitative analyses).

Shift analyses

Laboratory data will be summarized using shift tables where appropriate. Each subject's hematology, blood chemistry and urinalysis numeric values will be flagged as "low", "normal", or "high" relative to the normal ranges of the central laboratory or as "unknown" if no result is available. Each subject's urinalysis categorical values will be flagged as "positive" or "negative", or "unknown" if no value is available.

Shifts from baseline to high/low status will be presented for hematology, blood chemistry and urinalysis numeric parameters, and shifts from baseline to abnormal (positive) will be presented for urinalysis categorical parameters. Shift to low includes normal to low, high to low, and unknown to low; Shift to high includes normal to high, low to high, and unknown to high. Subjects need to have at least one post-baseline evaluation and a baseline value not low or high or positive (including missing) in order to be included in the analysis. A listing of laboratory normal ranges will be provided.

Grade analyses

Worst post-baseline grade will be summarized for each laboratory parameter in both exclusive way and cumulative way. Subjects need to have at least one post-baseline evaluation in order to be included in the analysis. Common Toxicity Criteria for Adverse Events v4.0.3 (CTCAE) published on 2010-06-14 will be used for grade determination. Grade determination is based solely on laboratory values not taking AEs into account.

Potentially Clinically Significant laboratory abnormalities analyses

For hematology, blood chemistry and urinalysis, the number of subjects with potentially clinically significant laboratory abnormalities post-baseline will be summarized for the parameters provided in Table 8. Subjects need to have at least one post-baseline evaluation and a baseline value not potentially clinically significant (including missing) in order to be included in the analysis.

Table 8: Criteria to Determine Potentially Clinically Significant (PCS) Laboratory Abnormalities

Clinical Laboratory Outlier Criteria		
Parameter name	**PCS Low**	**PCS High**
HEMATOLOGY		

Clinical Laboratory Outlier Criteria		
Parameter name	**PCS Low**	**PCS High**
White blood cells	<3.0 x 10^9/L	>16 x 10^9/L
Lymphocytes	<0.8 x 10^9/L	>12 x 10^9/L
Neutrophils	<1.5 x 10^9/L	>13.5 x 10^9/L
Monocytes	N/A	>2.5 x 10^9/L
Eosinophils	N/A	>1.6 x 10^9/L
Basophils	N/A	>1.6 x 10^9/L
Red blood cells	≤3.5 x 10^{12}/L	≥6.4 x 10^{12}/L
Hemoglobin - Females	≤95 g/L	≥175 g/L
Hemoglobin - Males	≤115 g/L	≥190 g/L
Hematocrit - Females	≤32%	≥54%
Hematocrit - Males	≤37%	≥60%
Platelet count	≤75 x 10^9/L	≥700 x 10^9/L
BLOOD CHEMISTRY		
Alanine aminotransferase (ALT)	N/A	>3 x ULN
Aspartate aminotransferase (AST)	N/A	>3 x ULN
Alkaline phosphatase (ALP)	N/A	>3 x ULN
Total bilirubin	N/A	>1.5 x ULN
Blood urea nitrogen (BUN)	N/A	≥10.7 mmol/L
Creatinine	N/A	≥176.8 umol/L
Sodium	≤126 mmol/L	≥156 mmol/L
Potassium	≤3 mmol/L	≥6 mmol/L
Chloride	≤90 mmol/L	≥118 mmol/L
Bicarbonate	≤16 mmol/L	≥35 mmol/L
Glucose	≤2.2 mmol/L	≥9.7 mmol/L
Calcium	≤2 mmol/L	≥3 mmol/L
Phosphorus	≤0.6 mmol/L	≥1.7 mmol/L
Albumin	≤25 g/L	≥625 g/L
Total protein	≤45 g/L	≥100 g/L
URINALYSIS		
Glucose	N/A	≥ ++++
Ketones	N/A	≥ ++++
Protein	N/A	≥ ++
ULN = upper limit of normal		

Potential serious hepatotoxicity

Potential serious hepatotoxicity is defined as ALT or AST > 3x ULN and total bilirubin > 2x ULN at any time post-baseline, not necessarily concurrent. A scatterplot of the maximum post-baseline ALT or AST value relative to ULN and maximum post-baseline total bilirubin value relative to ULN (not necessarily concurrent) for each subject will be provided. A line plot of ALT, AST, ALK and total bilirubin values over time for subjects with potential serious hepatotoxicity will be provided. In addition, subjects with ALT > 1x ULN, >3x ULN, >5x ULN, >10x ULN or >20x ULN, subjects with AST > 1x ULN, >3x ULN, >5x ULN, >10x ULN or >20x ULN, subjects with total bilirubin >1x ULN or >2x ULN, subjects with ALP >1x ULN or >1.5x ULN, and subjects with AST or ALT > 3x ULN post-baseline accompanied by concurrently elevated total bilirubin >1.5x ULN or > 2x ULN will be presented. Concurrent is defined as on the same day. A listing of subjects with potential serious hepatotoxicity will be provided.

4.5.5 C-SSRS Data

The Columbia Suicide Severity Rating Scale (C-SSRS) is an assessment that evaluates suicidal ideation and behavior. There are 5 "Yes/No" questions on suicidal ideation following the increasing severity order: (1) Wish to be dead, (2) Non-specific active suicidal thoughts, (3) Active suicidal ideation with any methods (not plan) without intent to act, (4) Active suicidal ideation with some intent to act, without specific plan, (5) Active suicidal ideation with specific plan and intent, and 6 "Yes/No" questions on suicidal behavior following the increasing severity order: (6) Preparatory acts or behavior, (7) Aborted attempt, (8) Interrupted attempt, (9) Actual attempt, (10) Suicidal behavior, (11) Suicide (only at post-baseline visits). Another "Yes/No" question of whether the subject has engaged in non-suicidal self-injurious behavior is also collected.

In the summary table for C-SSRS, number of subjects who answered "Yes" to each of the 11 questions post-baseline, subjects who answered "Yes" to at least one question for suicidal ideation, subjects who answered "Yes" to at least one question for suicidal behavior, and subjects who have engaged in non-suicidal self-injurious behavior will be presented. A listing of subjects with any suicidal ideation or behavior at baseline or post-baseline will be provided.

4.5.6 ECG Data

Shift from normal or unknown ECG at baseline to abnormal, not adverse event or abnormal, adverse event post-baseline ECG will be summarized for the placebo-controlled period. Subjects with abnormal post-baseline ECG status will be listed.

4.5.7 Vital Sign Data

Vital sign parameters include body temperature, systolic blood pressure, diastolic blood pressure, heart rate, respiration rate and weight. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes. The descriptive statistics for actual values and change from baseline will be summarized at each visit. Plot of mean vital sign values at each visit will be provided.

The analysis of vital signs will also focus on the incidence of clinically relevant outliers based on the following criteria. The incidence and percentage of clinically relevant outliers determined by each criterion will be summarized. A listing of subjects with clinically relevant vital signs will be provided.

Table 9: Criteria Used to Assess Potential Clinically Relevant Outliers in Vital Signs

Variable	Low	High
Systolic Blood Pressure	<90 mm Hg or ≥20 mm Hg decrease from Baseline (BL)	>180 mm Hg or ≥20 mm Hg increase from BL

Diastolic Blood Pressure	< 50 mm Hg or ≥15 mm Hg decrease from BL	>105 mg Hg or ≥15 mm Hg increase from BL
Heart Rate	<50 bpm or ≥ 15 bpm decrease from BL	>120 bpm or ≥ 15 bpm increase from BL
Temperature	>2 degree C decrease from BL	>38.5 C or >2 degrees C increase from BL
Respiration Rate	< 10 breaths per minute or ≥ 50% decrease from BL	>25 breaths per minute or ≥50% increase from BL
Weight	≥7% decrease from BL	≥7 % increase from BL
BL= baseline; bpm = beats per minute		

Visit windows for by visit summaries

For vital sign by visit summaries, the analysis visit should be defined using windows (see Table 10 below). If there is more than 1 value in the same analysis visit window for a certain parameter for a subject, then the closest record to the target visit day will be used for the by visit analysis. If there are 2 values in the same analysis visit window with the same distance from the target visit day for a certain parameter for a subject, then the record with the later date will be used for the by visit analysis.

Table 10: Visit Windows for Vital Sign by Visit Summaries

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 4	29	[2, 42]
Week 8	57	[43, 70]
Week 12	85	[71, 98]
Week 16	113	[99, 126]
Week 20	141	[127, 154]
Week 24	169	[155, 182]
Week 28	197	[183, 210]
Week 32	225	[211, 238]
Week 36	253	[239, 266]
Week 40	281	[267, 294]
Week 44	309	[295, 322]
Week 48	337	[323, 350]
Week 52	365	[351, 378]
Week 56	393	[379, 406]
Week 60	421	[407, 434]
Week 64	449	[435, 462]
Week 68	477	[463, 490]
Week 72	505	[491, 518]
Week 76	533	[519, the end day of the placebo-controlled period*]
* The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter LTE, and is the last day in study for subjects who do not enter LTE.		

4.6 Pharmacokinetics Analysis

The PK analysis population will be used for the description of the concentration-time profiles and for the estimation of PK parameters. Randomization treatment groups will be used for

PK analysis. Tables and figures, if not otherwise specified, will be presented by treatment group stratified by ApoE status (3 columns under each treatment group: ApoE ε4+, ApoE ε4- and total; analysis display B in Appendix 6.1). Listings will be presented by treatment group stratified by ApoE status.

PK evaluation will be based on the concentration of aducanumab in serum samples collected prior to infusion and between 10 and 60 minutes after completion of the infusion and line flush for the visits specified per protocol.

Concentrations of aducanumab that are below the limit of quantification (BLQ) will be imputed as 0. When summarizing concentrations or PK parameters in serum, a minimum of 2 values are required to show the arithmetic mean and geometric mean, and at least 3 values are required to show the standard deviation and coefficient of variation.

4.6.1 Serum Concentration Profile

Serum concentration data will be summarized by nominal visit. Number of evaluable subjects, arithmetic mean, standard deviation, median, 25% and 75% quartiles, minimum, maximum, geometric mean, and coefficient of variation will be presented at each visit. A listing of individual concentration data will be provided.

A semi-logarithmic plot of the mean serum concentration-time curves of aducanumab from first visit to last visit through nominal times will be provided.

4.6.2 Serum PK Parameters

Two PK parameters C_{max} and C_{min} will be computed by noncompartmental methods, as data permit, from serum concentration-time data:

Parameter	Definition	Units
C_{max}	Observed maximum serum aducanumab concentration	ug/mL
C_{min}	Observed minimum serum aducanumab concentration	ug/mL

Number of evaluable subjects, arithmetic mean, standard deviation, median, 25% and 75% quartiles, minimum, maximum, geometric mean, and coefficient of variation will be presented for the PK parameters.

4.6.3 Subgroup analysis for protocol version 4

Due to the change in maximal dose from 6 mg/kg to 10 mg/kg for ApoE ε4 carrier high dose group in protocol version 4, not all subjects have had opportunity to receive the protocol specified high dose (6 doses in titration before receive 10mg/kg) in the placebo-controlled period. Summary tables for serum concentration and PK parameters will be provided for ApoE ε4 carriers who were randomized to the high dose group, stratified by the expected number of doses at 10 mg/kg (categories of 0, 1-6, 7-13, 14, and a total column of having at least one dose) a subject would have received based on the first infusion date and the date consenting to protocol version 4.

4.7 Immunogenicity Analysis

4.7.1 Background

Definition of baseline value

Baseline value is defined as the latest immunogenicity data collected prior to the first dose. If no immunogenicity data are collected prior to the first dose, baseline value is missing and will be imputed as anti-drug antibody negative for immunogenicity analyses.

Treatment-emergent anti-aducanumab antibody positive responses

Post-baseline positive anti-aducanumab antibody responses are defined as treatment-emergent if a subject is either (1) antibody negative at baseline; or (2) antibody positive at baseline but the post-baseline antibody response is more than 2-fold increase in titer compared to the baseline response.

Persistent and transient positive responses for the placebo-controlled period

Subjects with treatment-emergent positive anti-aducanumab antibody responses in the placebo-controlled period will be further classified as transient positive, if only a single positive evaluation occurs or more than 1 positive evaluation but occur with < 112 days (16 weeks) apart, or as persistent positive, if more than one consecutive positive evaluation occurs ≥ 112 days (16 weeks) apart or a positive evaluation occurs at the last available time point with no further negative results available (including long-term extension).

4.7.2 Immunogenicity analysis

Immunogenicity population will be used to analyze immunogenicity data. Safety treatment groups will be used for immunogenicity analysis. Tables will be presented by treatment group (placebo, low dose, high dose and BIIB037 total; analysis display A in Appendix 6.1). Listings will be presented by treatment group stratified by ApoE status.

A summary table of subjects with treatment-emergent positive anti-aducanumab antibody responses results will be provided. The number and percentage of anti-aducanumab positive responses will be summarized at each visit and at any time post-baseline. Subjects with persistent response and subjects with transient response will be presented. A listing of subjects with anti-aducanumab antibody positive results will also be provided.

Visit windows for by visit summaries

For immunogenicity by visit summaries, the analysis visit should be defined using visit windows (see Table 11Table 7 below). If there is more than 1 value in the same analysis visit window for a subject, then the closest record to the target visit day will be used for the by visit analysis. If there are 2 values in the same analysis visit window with the same distance

from the target visit day for a certain parameter for a subject, then the record with the later date will be used for the by visit analysis. If there are 2 values on the same day for a certain parameter for a subject, then the record with the later time will be used for the by visit analysis.

Table 11: Visit Windows for Immunogenicity by Visit Summaries

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 24	169	[2, 196]
Week 32	225	[197, 308]
Week 56	393	[393, 470]
Week 78	547	[470, the end day of the placebo-controlled period*]
* The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter LTE, and is the last day in study for subjects who do not enter LTE.		

4.8 Additional Exploratory Endpoints

4.8.1 Biomarker

Analyses for structural MRI, tf-fMRI, ASL-MRI, tau PET, CSF biomarkers and blood biomarkers will be specified in a separate SAP for biomarker analysis.

4.8.2 Health Outcomes

Analyses for informant/care partner's own EQ-5D index-score (IR-I) and CAM will be provided in a separate document.

5 INTERIM ANALYSIS

An interim analysis will occur after approximately 50% of the subjects have had the opportunity to complete the Week 78 visit for both 221AD301 and 221AD302. To maintain the integrity of the study in the event of the interim analysis, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim analysis. The IDMC will review the unblinded results of the interim analysis provided by the independent group and will make a recommendation to Biogen based on pre-specified criteria.

An interim analysis for futility of the primary endpoint will be performed to allow early termination of the studies if it is evident that the efficacy of aducanumab is unlikely to be achieved. The futility criteria will be based on conditional power, which is the chance that the primary efficacy endpoint analysis will be statistically significant in favor of aducanumab at the planned final analysis, given the data at the interim analysis. The conditional power is calculated assuming that the future unobserved effect is equal to the maximum likelihood estimate of what is observed in the interim data:

$$CP\left(Z(1) \geq Z_\alpha \middle| Z(t)\right) = 1 - \phi\left(\frac{Z_\alpha\sqrt{n_2} - Z(t)\sqrt{n_1}}{\sqrt{n_2 - n_1}} - \frac{Z(t)\sqrt{n_2 - n_1}}{\sqrt{n_1}}\right)$$

where t is the fraction of information and $Z(t)$ is the observed Z-statistic at the interim analysis, $Z(1)$ is the Z-statistic and α is the type I error at the final analysis, n_1 and n_2 are the number of subjects at the interim and at the final analysis, respectively.

The futility decision will primarily be based on the conditional power for the primary efficacy endpoint. The study will not be considered as futile unless both studies 221AD301 and 221AD302 have conditional power for the primary efficacy endpoint less than 20% in both the high-dose and low-dose treatment groups. Given the insufficient knowledge of aducanumab's potential effects on various functional/cognition endpoints or in certain subgroups at the present time, other data in addition to the pre-specified futility criteria will be considered as well, and the IDMC may recommend the studies to be continued as planned based on the weight of the evidence.

An interim analysis for superiority may be performed, to allow the possibility to demonstrate the treatment effect early. If an interim analysis for superiority is performed, the O'Brien-Fleming stopping boundary will be used. If an interim analysis for superiority is not performed, then no alpha adjustment will be used for the final analysis after all subjects have had the chance to complete the Week 78 visit.

6 APPENDIX

6.1 Analysis Display

Analysis display A

Placebo	BIIB037 low dose	BIIB037 high dose

Analysis display B

Placebo			BIIB037 low dose			BIIB037 high dose		
ApoE e4+ placebo	ApoE e4- placebo	Total	ApoE e4+ 3 mg/kg	ApoE e4- 6 mg/kg	Total	ApoE e4+ 10 mg/kg	ApoE e4- 10 mg/kg	Total

6.2 Protocol Deviation Classification

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

6.3 Implementation of the Copy Increment from Reference and Pattern Mixture Model

6.3.1 Copy Increment from Reference

The dataset will first be imputed to monotone missing using PROC MI with the MCMC and impute=monotone option. Imputation will be carried out 1000 times and any internal missing observations, including missing baseline covariates and intermediate missing in the response variable will be replaced with the average across all imputations.

For the resulted data with monotone missing, the following steps will be used to create imputed datasets:

(1) Data from all patients will be used to fit a multivariate normal distribution with unstructured mean and unstructured variance using a Bayesian approach with a noninformative prior for the mean and a conjugate prior for the variance covariance matrix.

(2) Draw a pseudo-independent sample for the linear predictor parameters and the covariance parameters from the joint posterior distribution obtained in step (1). Both steps (1) and (2) will be done using PROC MCMC in SAS.

(3) Use the linear predictor parameters and the covariance parameters obtained in step (2) to construct new mean vectors separately for each treatment group (placebo, aducanumab low dose, aducanumab high dose). Specifically, the newly constructed mean vector for someone on treatment group T whose last observed visit was visit k is calculated as

$$\mu_T^{(k)} = \begin{cases} \mu_{i,T}, & if\ i \le k \\ \mu_{k,T} - \mu_{k,P} + \mu_{i,P}, & if\ i > k \end{cases}$$

Here P represents the placebo group. For patients with no post-baseline records, or patients on the placebo group, the newly constructed mean vector is the same as the placebo mean.

(4) Using $\mu_T^{(k)}$ from step (3) and covariance parameters from step (2), find the conditional normal distribution of the visit with missing data, and use this conditional distribution to impute the missing data.

6.3.2 Pattern Mixture Model

Subjects will be assigned one of the following three patterns:

1. Completer: subjects with no missing data at Week 26, 50 and 78
2. Subjects who withdrew due to reasons that may be related to efficacy, including consent withdrawn, withdrawal by parent/guardian, investigator decision, loss of capacity, change of treatment, and disease progression;
3. All the other subjects with missing data.

The dataset will first be imputed to monotone missing using PROC MI with the MCMC and impute=monotone option. Imputation will be carried out 1000 times and any internal missing observations, including missing baseline covariates and intermediate missing in the response variable will be replaced with the average across all imputations.

For the resulted data with monotone missing, the following steps will be used to create imputed datasets:

(1) Subset subjects in pattern 1 and pattern 2, and impute the missing data using the copy increment from reference method described in Section 6.3.1.
(2) Subset subjects in pattern 1 and pattern 3, and impute the missing data using PROC MI with the MONOTONE REG option.
(3) Combined datasets obtained in steps (1) and (2).

7 REFERENCES

Carpenter JR, Roger JH, Kenward MG. Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat. 2013;23(6):1352-71.

Hansen RA, Gartlehner G, Lohr KN, et al. Functional outcomes of drug treatment in Alzheimer's disease: A systematic review and meta-analysis. Drugs & aging. 2007;24(2):155-67.

ICH E9 (R1): Addendum to statistical principles for clinical trials on choosing appropriate estimands and defining sensitivity analyses in clinical trials. Endorsed by the ICH Steering Committee. 2014.

ICH E9 (R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials. European Medicines Agency. 2017.

Li, J. and Barlas, S. Divergence effect analysis in disease-modifying trials. Statistics in Biopharmaceutical Research. 2017; 9: 390-398.

Li, K. H. (1988), "Imputation Using Markov Chains," *Journal of Statistical Computation and Simulation*, 30, 57–79.

Little, R.J.A. (1993). Pattern‐mixture models for multivariate incomplete data. *Journal of the American Statistical Association, 88* , 125-134.

Little, R.J.A. (1994). A class of pattern‐mixture models for normal missing data. *Biometrika, 81*, 471-483.

Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993;43(11):2412–2414.

Mueller SG, Weiner MW, Thal LJ, et al. The Alzheimer's Disease Neuroimaging Initiative. In: Pettrella JR, Doraiswamy PM, eds. Neuroimaging Clinics of North America: Alzheimer's Disease: 100 Years of Progress. Philadelphia: Elsevier Saunders; 2005:869–877.

Rockwood K. The measuring, meaning and importance of activities of daily living (ADLs) as an outcome. Int Psychogeriatr. 2007;19(3):467-82. Epub 2007/03/15.

Rubin, D. B. (1976) “Inference and missing data.” Biometrika, 63(3), 581-592.

Rubin D.B. Multiple Imputation for Nonresponse in Surveys. John Wiley & Sons. 1987.

Schafer J.L. Analysis of Incomplete Multivariate Data. Chapman and Hall, New York. 1997.

Tractenberg RE, Weiner MF, Cummings JL, Patterson MB, Thal LJ. Independence of changes in behavior from cognition and function in community-dwelling persons with

Alzheimer's disease: a factor analytic approach. J Neuropsychiatry Clin Neurosci. 2005;17(1):51–60.

van Ginkel, J. R., Sijtsma, K., van der Ark, L. A., & Vermunt, J. K. (2010). Incidence of missing item scores in personality measurement, and simple item-score imputation. *Methodology: European Journal of Research Methods for the Behavioral and Social Sciences, 6*(1), 17-30.

Yan, X., Lee, S., and Li, N. (2009), "Missing data handling methods in medical device clinical trials," Journal of Biopharmaceutical Statistics, 19(6), 1085-1098.

Zucker, D. M., Wittes, J. T., Schabenberger, O. and Brittain, E. Internal pilot studies II: comparison of various procedures. Statistics in Medicine. 1999;18: 3493–3509.

STATISTICAL ANALYSIS PLAN
Addendum

Product Studied: Aducanumab
Protocol Number: 221AD302

A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease

Protocol Version: Version 6.0
Date of Protocol: 28 Jun 2018

Date of Statistical Analysis Plan Addendum: 4 Nov 2019, Final V1.0

Written By:	PPD	4 Nov 2019 Date
		04 Nov 2019 Date
Approved By:		4 Nov 2019 Date
		4 Nov 2019 Date
		4 Nov 2019 Date

1 Modifications for Efficacy Analysis

The primary analysis will be conducted in the intent-to-treat (ITT) population, excluding data collected after 20 March 2019. The mixed model repeated measures (MMRM) model remains the same as before.

Unless otherwise specified, data collected after 20 March 2019 will be excluded for all the analysis of the primary and secondary endpoints, and the tertiary endpoints for efficacy and quality of life.

The following analyses will be conducted for the primary and secondary endpoints as supplementary analysis.

- Opportunity-to-Complete (OTC) analysis:
  The MMRM model in primary analysis will be repeated in the OTC population, defined as the ITT population that have had the opportunity to complete Week 78 by 20 March 2019.
- ITT analysis during the double-blind period:
  The MMRM model in primary analysis will be repeated in the ITT population with all the data collected until 17 April 2019 (Biogen released treatment assignments to IQVIA team on 18 April 2019 to be distributed to site upon request). Efficacy data collected up to 17 April 2019 will be mapped to analysis visits according to the pre-specified analysis definition (Table 3 in SAP v1.0 Section 4.3.1).

  The assessments collected after the futility announcement (21 March 2019) may deviate from the efficacy data schedule defined in protocol. Given the width of the pre-specified analysis visit window, an assessment may be mapped to an analysis visit even though the data collection day is far away from the target day of that analysis visit. In addition to the above analysis using the pre-specified analysis visits, analysis will also be conducted after data collected post 20 March 2019 being extrapolated to the closest analysis visit target day if the difference between the data collection day and the visit window target day exceeds 28 days. For example, if a subject's CDR-SB at the end-of-treatment (EOT) visit (after 20 March 2019) was collected on Day 480, the score will be extrapolated to Day 547 (the target day of Week 78) for analysis.
- Uncensored ITT analysis:
  The MMRM model in primary analysis will be repeated in the ITT population with all the data collected during the study, using the pre-specified analysis visits without extrapolation and using the analysis visits corrected by extrapolation, respectively.

Rationale for modifications:

The study was terminated on 21 March 2019 after a futility analysis. The treatment was stopped immediately upon the futility announcement for all subjects. Although assessments for efficacy and quality of life continued to be collected after the futility announcement at the

end-of-treatment visit and safety follow-up visit, these data may introduce bias due to assessments possibly being altered by knowledge of the futility declaration. The data collected after 20 March 2019 may also deviate from the planed schedule for efficacy/quality of life defined in protocol. Based on these considerations, the above modifications are made to the primary efficacy analysis, to include as many subjects and data as possible for analysis while minimizing potential bias in the results. The OTC analysis, ITT analysis during the double-blind period, and the uncensored ITT analysis are added to evaluate the robustness of the primary analysis results.

2 Other Modifications

The following change is in response to FDA's comments on SAP version 1.

- If the unstructured covariance matrix results in a lack of convergence in the mixed model for repeated measures (MMRM) and a structured covariance matrix is used, we will use the sandwich estimator to obtain the variance of the treatment effect estimator.

1. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

1.1. Changes in the Conduct of the Study

Participant enrollment into Study 221AD301 began under Version 1 dated 09 April 2015. Subsequently, there have been 5 amendments to the protocol, of which 4 amendments were submitted globally. Version 2 was not submitted globally and no participants were enrolled under this version. Protocol Version 6 (dated 28 June 2018) was in effect when the study was terminated.

A high-level summary of key changes to the global protocol is provided in Table 1, including key changes in ARIA management and changes affecting aducanumab dosing.

1.2. Changes in the Planned Analyses

The SAP Version 1 was finalized on 11 September 2018. A SAP Addendum was finalized on 04 November 2019, prior to database lock. The SAP addendum documented the changes in the primary analysis and additional supplementary analyses as a result of the study termination. More specifically, the primary efficacy analysis excluded data collected after 20 March 2019; the supplementary analyses that included data after 20 March 2019 were added to evaluate the robustness of the primary analysis.

Table 1: Summary of Key Changes to Protocol 221AD301

Version[1]	Key Changes to ARIA Management	Other Key Changes
Version 1 (dated 09 April 2015) to Version 3 (dated 21 July 2016)	• To allow participants who suspend dosing after a first observance of ARIA to (a) restart at the same dose (rather than at the next lower dose per Version 1) after ARIA resolution and (b) titrate up to the originally assigned dose (rather than continue on the next lower dose for the duration of the study) • Removed requirement to permanently discontinue treatment after severe symptomatic ARIA or serious ARIA ("other medically important" criteria only); instead, in such participants, dosing could be suspended and then resumed at the same dose after ARIA and symptoms resolved or stabilized. • Regarding the management of recurrent ARIA, the amendment (a) allowed participants who had suspended dosing after a second episode to restart dosing, after ARIA resolution, at the next lower dose and continue uptitration (rather than remaining on the restart dose as in Version 1) and (b) required treatment discontinuation after 3 ARIA episodes (rather than requiring a third dose reduction with Sponsor approval).	

Version[1]	Key Changes to ARIA Management	Other Key Changes
Version 3 (dated 21 July 2016) to Version 4 (dated 24 March 2017)	• To allow ApoE ε4 carrier participants randomized to aducanumab high-dose to receive the same aducanumab high-dose regimen already received by ApoE ε4 noncarriers (i.e., per this amendment, the high dose for carriers was changed from 6 to 10 mg/kg, which was also the high-dose for noncarriers).	
Version 4 (dated 24 March 2017) to Version 5 (dated 18 September 2017)		• To update the percentage of primary endpoint data estimated to be available at the time of a potential blinded sample size re-estimation. • To provide additional details on the planned sample size re-estimation (including the maximum potential sample size). • To add information on an additional concentration and formulation for aducanumab used in the study.
Version 5 (dated 18 September 2017) to Version 6 (dated 28 June 2018)	• To reflect the agreement of the data monitoring committee that the characteristics or outcomes of the first event and recurrent events of ARIA were similar, the management of recurrent ARIA was modified so that a third episode of ARIA that requires dose suspension will no longer require study treatment discontinuation, and after recurrent ARIA resolves or stabilizes, dosing will resume at the same dose.	• To extend the study such that participants nearing study completion under Protocol Version 5 can continue in the study and receive treatment until either the participant's End of Treatment Visit at Week 338 (an additional 3 years of treatment) or until the last participant has had his or her Week 182 Visit, whichever occurs first. • To update adjust the sample size consistent with an increase from 450 to 535 participants per treatment group following

Version[1]	Key Changes to ARIA Management	Other Key Changes
		the blinded sample size re-estimation to ensure adequate power to detect a mean treatment effect of 0.5 for the primary endpoint, as prespecified in Protocol Version 1.

[1] No participants were consented under Protocol Version 2 and as a result, changes from Version 1 to Version 2 are not provided.

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PROTOCOL NUMBER: 221AD301

PHASE OF DEVELOPMENT: 3

PROTOCOL TITLE: A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease

EUDRA CT NO: **2015-000966-72**

DATE: 09 April 2015
Version 1.0
Final

SPONSOR SIGNATURE

Protocol 221AD301 was approved by:

PPD

09 APRIL 2015

Date

Biogen MA Inc.

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Biogen may transfer any or all of its study-related responsibilities to a contract research organization (CRO) and other third parties; however, Biogen retains overall accountability for these activities.

2. LIST OF ABBREVIATIONS

12F6A	recombinant, human anti-β-amyloid immunoglobulin G_1 monoclonal antibody with an amino acid sequence identical to aducanumab , produced in a different Chinese hamster ovary cell line
^{18}F-florbetapir	Also known as florbetapir-fluorine-18 or ^{18}F-AV-45 (amyloid ligand; trade name Amyvid)
Aβ	β-amyloid
AA	Alzheimer's Association
AD	Alzheimer's disease
ADA	antidrug antibodies
ADAS-Cog 13	Alzheimer's Disease Assessment Scale - Cognitive Subscale (13 items)
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment version)
AE	adverse event
ALT	alanine aminotransferase
ApoE	apolipoprotein E
ApoE ε4	apolipoprotein E4
ARIA	amyloid related imaging abnormalities
ARIA-E	amyloid related imaging abnormality-edema
ARIA-H	amyloid related imaging abnormality-hemorrhage or superficial siderosis
ASL-MRI	arterial spin labeling magnetic resonance imaging
AST	aspartate aminotransferase
CDR	Clinical Dementia Rating
ch12F6A	murine IgG_{2a} chimeric version of 12F6A or aducanumab
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	diastolic blood pressure
DHA	Directions for Handling and Administration
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
EDC	electronic data capture
EOT	End of Treatment
EQ-5D	EuroQol health status measure
ET	Early Termination
FU	follow-up

GCP	Good Clinical Practice
HbA_{1c}	glycosylated hemoglobin
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
Ig	immunoglobulin
IR	informant rated
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous(ly)
IWG	International Working Group
LTE	long-term extension
LP	lumbar puncture
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-model repeated measures
MMSE	Mini-Mental State Examination
MOCA	Montreal Cognitive Assessment
mPDQ-20	Perceived Deficits Questionnaire-20 modified version
MRI	magnetic resonance imaging
NIA	National Institute on Aging
NPI-10	Neuropsychiatric Inventory-10
PET	positron emission tomography
PK	pharmacokinetic(s)
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
SABR	Safety and Benefit-Risk
SAE	serious adverse event
SAP	statistical analysis plan
SB	sum of boxes
SBP	systolic blood pressure
SD	standard deviation
SR	subject rated
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
tf-fMRI	task free functional MRI
UV	unscheduled visit

3. SYNOPSIS

Protocol Number:	221AD301
Protocol Title:	A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease
Version Number:	1.0
Name of Study Treatment:	Aducanumab (BIIB037)
Study Indication:	Alzheimer's Disease
Study Rationale:	The purpose of this Phase 3 study is to assess the efficacy and safety of aducanumab compared with placebo in subjects with early Alzheimer's Disease (AD), including mild cognitive impairment (MCI) due to AD and a subset of mild AD. Aducanumab is a human monoclonal antibody that recognizes aggregated forms of β-amyloid (Aβ), including soluble Aβ oligomers and deposited fibrillar Aβ. Interim analyses of the ongoing multiple dose study (Study 221AD103) have demonstrated target engagement, a pharmacodynamic effect on amyloid reduction, and an effect on the Clinical Dementia Rating (CDR)-Sum of Boxes (SB) and Mini-Mental State Examination (MMSE) suggestive of a reduction in the progression of clinical impairment for aducanumab-treated subjects. These results along with the observed safety and tolerability profile warrant further Phase 3 investigation of aducanumab in a patient population spanning the early stages of the AD continuum.
Phase of Development:	3
Study Objectives and Endpoints (placebo-controlled period of the study):	The primary objective of the study is to evaluate the efficacy of monthly doses of aducanumab in slowing cognitive and functional impairment as measured by changes in the CDR-SB score as compared with placebo in subjects with early AD. The primary endpoint that relates to this objective is the change from baseline in CDR-SB score at Week 78

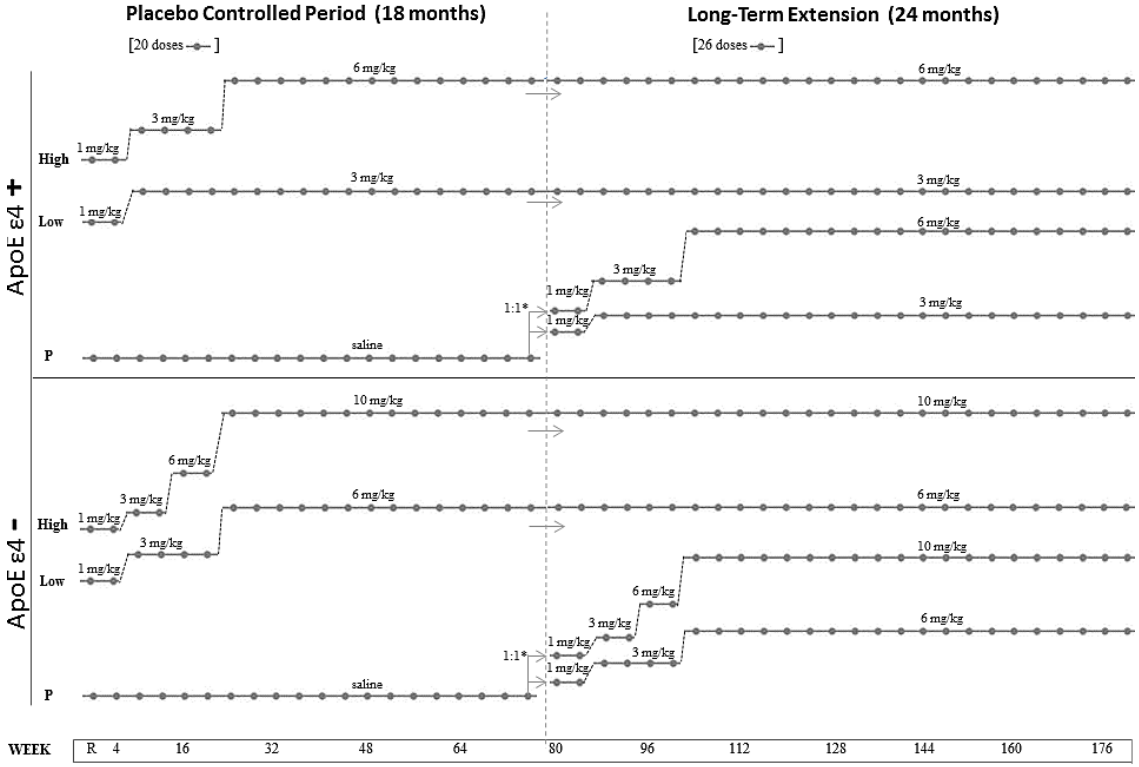
	Secondary objectives and endpoints are as follows: To assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by • MMSE – Change from baseline in MMSE score at Week 78 • Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13] – Change from baseline in ADAS-Cog 13 at Week 78 • Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI] – Change from baseline in ADCS-ADL-MCI score at Week 78 Tertiary objectives of this study are listed in Section 6.3.1. Tertiary endpoints of this study are listed in Section 6.3.2.
Study Objectives and Endpoints (Dose-Blind Long-Term Extension):	The objectives are to evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD, and to evaluate the long-term efficacy of aducanumab treatment as measured by clinical, radiological and additional assessments reported by the subject and informant/care partner. Endpoints for the LTE period of the study are listed in Section 6.4.2.
Study Design:	Multicenter, randomized study with an 18-month double-blind, placebo-controlled period followed by an optional 24-month dose-blind, LTE period
Study Location:	Approximately 150 sites globally
Number of Planned Subjects:	Approximately 1350 subjects will be enrolled
Study Population:	This study will be conducted in subjects with early AD, including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD according to NIA-AA

	criteria. Subjects must be positive for amyloid pathology as measured by amyloid positron emission tomography scan. Subjects must be 50 to 85 years old, and apart from the clinical diagnosis of early AD, they must be in good health as determined by the Investigator, based on medical history and the Screening assessments. Subject enrollment will be monitored so that approximately 60% to 70% ApoE ε4 carriers are enrolled. Enrollment will also be monitored, via interactive response technology (IRT), such that subjects with mild AD represent a small percentage of the total enrolled in the trial. Detailed criteria are described in Section 8.
Treatment Groups:	For the 18-month placebo-controlled period of the study and based upon their ApoE ε4 carrier status, subjects will be assigned to 1 of 3 treatment groups (450 subjects each) in a 1:1:1 ratio (aducanumab low dose: aducanumab high dose: placebo) as follows: **ApoE ε4 carrier** **Low dose (3 mg/kg)** **High dose (6 mg/kg)** **Placebo** **ApoE ε4 non-carrier** **Low dose (6 mg/kg)** **High dose (10 mg/kg)** **Placebo** After completion of the placebo-controlled period, subjects may enter a 24-month dose-blind LTE study during which all subjects will receive aducanumab.
Duration of Treatment and Follow-up:	Study duration for each subject participating in the placebo-controlled period only will be approximately 102 weeks (up to an 8 week Screening Period, 76 weeks of placebo or aducanumab dosing, and 18 weeks of follow-up). For subjects who enter the optional LTE, the total duration will be approximately 206 weeks or 47 months (up to an 8 week Screening Period, 76 weeks of placebo or aducanumab dosing, 4 weeks of follow-up, 100 weeks of dose-blind aducanumab dosing, and 18 weeks of follow-up).

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY 221AD301

4.1. Study Schematic

Figure 1: Study Design



ApoE ε4 +/- = apolipoprotein E4 positive/negative; R = randomization date

*Subjects who are assigned to placebo during the placebo-controlled period and are continuing into the LTE will be randomized in a 1:1 ratio to high and low dose aducanumab treatment (based upon their ApoE ε4 carrier status).

4.2. Schedule of Events

Table 1: Placebo-Controlled Period Schedule

Study Week	Screening (≤ 60 days before Day 1)[1]																											UV for a change in AD medication	FU/ET[2]
				Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	50	52	56	60	64	68	72	76	78 (EOT)		94
Study Day	V1	V2	V3	1	29 ± 3	57± 3	85 ±3	113 ±3	141 ±3	169 ±3	183 ±3	197 ±3	225 ±3	253 ±3	281 ±3	309 ±3	337 ±3	351 ±3	365 ±3	393 ±3	421 ±3	449 ±3	477 ±3	505 ±3	533 ±3	547 ±3		659 ±7
Initial Screening Consent[3]	X																												
Full Informed Consent[4]	X																									X[5]			
Eligibility Criteria	X			X																						X[5]			
Medical History	X																												
Alcohol/Drug Screen	X																												
HbA_{1c}	X																												
HIV/Hepatitis/ Coagulation	X																												
ApoE genotyping	X																												
DNA (optional)[6]	X																												
Height	X																												
Body Weight	X			X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X			X
Serum Pregnancy Test[7]	X																												
Urine Pregnancy Test[7]				X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X			X
Physical Examination	X						X			X							X							X		X		X

Study Week	Screening (≤ 60 days before Day 1)[1]			Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	50	52	56	60	64	68	72	76	78 (EOT)	UV for a change in AD medication	FU/ET[2]
Study Day	**V1**	**V2**	**V3**	**1**	**29 ± 3**	**57± 3**	**85 ±3**	**113 ±3**	**141 ±3**	**169 ±3**	**183 ±3**	**197 ±3**	**225 ±3**	**253 ±3**	**281 ±3**	**309 ±3**	**337 ±3**	**351 ±3**	**365 ±3**	**393 ±3**	**421 ±3**	**449 ±3**	**477 ±3**	**505 ±3**	**533 ±3**	**547 ±3**		**659 ±7**
Neurological Examination	X						X			X							X							X		X		X
12-lead paper ECG	X									X							X							X		X		X
Vital Signs[8]	X			X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X			X
Hematology, Blood Chemistry and Urinalysis	X			X						X							X							X		X		X
Randomization				X																								
Study Drug Infusion				X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X			
Anti-aducanumab Ab[9]				X						X							X							X		X		X
Aducanumab Concentration[10]				X[11]	X[11]		X[11]	X	X[11]	X[11]		X[11]	X						X[11]	X					X			
Biomarkers (RNA, serum, and plasma)[12]	X									X							X							X		X		X
CSF Collection (optional)	X[13]																									X		
Amyloid PET[14]			X								X															X		
RBANS	X																											
CDR	X										X							X								X	X	X
MMSE	X										X							X								X	X	X
ADCS-ADL-MCI		X[15]									X							X								X	X	X
ADAS-Cog 13		X[15]									X							X								X	X	X

Study Week	Screening (≤ 60 days before Day 1)[1]			Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	50	52	56	60	64	68	72	76	78 (EOT)	UV for a change in AD medication	FU/ET[2]
Study Day	V1	V2	V3	1	29 ± 3	57± 3	85 ±3	113 ±3	141 ±3	169 ±3	183 ±3	197 ±3	225 ±3	253 ±3	281 ±3	309 ±3	337 ±3	351 ±3	365 ±3	393 ±3	421 ±3	449 ±3	477 ±3	505 ±3	533 ±3	547 ±3		659 ±7
NPI-10		X 15									X							X								X		X
EQ-5D (SR)		X 16									X							X								X		X
EQ-5D (IR-S)		X 16									X							X								X		X
EQ-5D (IR-I)		X 16									X							X								X		X
mPDQ-20		X 16									X							X								X		X
Caregiver Burden Questionnaire		X 16									X							X								X		X
C-SSRS				X															X							X		X
AE Reporting				Monitor and record continuously throughout the study																								
Concomitant therapy and procedures				Monitor and record continuously throughout the study																								
SAE reporting				Monitor and record continuously throughout the study																								

AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); ApoE = apolipoprotein E; CDR = Clinical Dementia Rating scale; CSF: cerebrospinal fluid ; C-SSRS = Columbia Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) =EQ-5D, subject self-reported; EOT = End of Treatment; ET = Early Termination; FU = Follow-up; HbA1c = glycosylated hemoglobin; HIV = human immunodeficiency virus; MMSE = Mini-Mental State Examination; mPDQ-20 = modified Perceived Deficits Questionnaire-20; MRI = magnetic resonance imaging; NPI-10 = Neuropsychiatric Inventory; PET = positron emission tomography; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; RNA = ribonucleic acid; SAE = serious adverse event; UV = unscheduled visit; V1, V2, V3 = Screening Visit 1, Screening Visit 2 and Screening Visit 3

[1] Examinations required for assessment of subject eligibility must be performed at V1. Brain MRI (Table 2) should only be performed once the subject meets eligibility criteria at V1. Amyloid PET should only be performed if the subject meets eligibility criteria at V1 and V2.

[2] Visit to be completed in cases of early termination or for subjects who do not enroll in the long-term extension.
[3] Subjects may sign this optional form for an initial screening which allows administration of the RBANS, CDR and MMSE only.
[4] All subjects must sign this informed consent, including subjects who have signed the initial screening consent once they have met the RBANS, CDR and MMSE eligibility criteria.
[5] Only for subjects entering the long-term extension.
[6] Can be collected at any point during and after Screening.
[7] Required for women of child bearing potential only (See Section 15.5).
[8] Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes.
[9] Sample collection for anti-aducanumab antibody will be performed prior to blood collection for aducanumab concentration or study drug infusion
[10] Blood sampling for aducanumab concentration will be performed prior to infusion.
[11] One additional blood sample for aducanumab concentration will be collected between 10 and 60 minutes after completion of the infusion and line flush
[12] Sample will be collected prior to infusion (where applicable).
[13] May be collected at any point in time during Screening after eligibility at V1 is confirmed but if collected on the same day as an MRI, it should be collected after the MRI is performed.
[14] Screening PET is required for all subjects, PET at Week 26 and Week 78 will only be conducted in selected sites for subjects who are participating in the PET cohort.
[15] Must be performed within 14 days of V1, but not on the same day as the screening RBANS, CDR or MMSE.
[16] May be performed at any point during screening after the subject has met eligibility criteria on the RBANS, CDR and MMSE.

Table 2: Brain MRI, Aria Management, and Follow-up Phone Call Schedule During the Placebo-Controlled Period

Study Week	Screening[1] (≤ 60 days before Day 1)			Placebo-Controlled Period												Unscheduled Visit for ARIA[2]	FU[3] /ET
				Day 1	2	6	10	14	18	22	26	30	42	54	78		94
Study Day	V1	V2	V3	1	15±3	43±3	71±3	99±3	113±3	155±3	183±3	211±3	295±3	379±3	547±3		826 ±7
Follow-up Phone Call					X	X	X	X	X	X	X	X					
Brain MRI[4]		X						X		X		X	X	X	X	X	X
Aducanumab Concentration[5]										X		X		X			X
MOCA				X												X	

ARIA = amyloid related imaging abnormalities; ET = Early Termination; FU = follow-up; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; V1, V2, V3 = Screening Visit 1, Screening Visit 2, and Screening Visit 3

[1] Brain MRI (V2) will not be performed until the subject has met the eligibility criteria and has acceptable laboratory tests from V1.

[2] Details on ARIA management are in Section 7.2.

[3] Assessments to be completed as part of an ET Visit or for subjects not enrolling into the long-term extension.

[4] Arterial spin labeling MRI and task free functional MRI will be performed only at a subset of sites.

[5] One sample will be collected within 2 days after the MRI visit. Exact collection date and time will be captured for all pharmacokinetic blood samples on a specified case report form.

Table 3: Long-Term Extension Schedule

Study Week	80	84	88	92	96	100	104	108	112	116	120	124	128	132	136	140	144	148	152	156	160	164	168	172	176	180	182 (EoT)	UV for a change in AD medication	FU /ET
Study Day	561 ±5	589 ± 5	617 ± 5	645 ± 5	673 ± 5	701 ± 5	729 ± 5	757 ± 5	785 ± 5	813 ± 5	841 ± 5	869 ± 5	897 ± 5	925 ± 5	953± 5	981± 5	1009 ±5	1037 ±5	1065 ±5	1093 ±5	1121 ± 5	1149 ± 5	1177 ± 5	1205 ± 5	1233 ± 5	1261 ±5	1275± 5		1387±7
Randomization	X[1]																												
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Urine Pregnancy Test[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Physical Examination				X			X						X						X						X		X		X
Neurological Examination				X			X						X						X						X		X		X
12-lead Paper ECG							X						X						X						X				X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hematology, Blood Chemistry and Urinalysis							X						X						X						X				X
Anti-aducanumab Ab[3]	X						X						X						X						X		X		X
Biomarkers (RNA, serum, and plasma)[3]							X						X						X						X				X
Aducanumab Concentration[3]	X						X						X						X						X		X		X
Study Drug Infusion	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
CSF Collection (optional)[4]														X													X		
Amyloid PET[5]														X													X		
CDR [6]							X							X							X						X	X	X
MMSE[6]							X							X							X						X	X	X
ADAS-Cog 13[6]							X							X							X						X	X	X
ADCS-ADL-MCI[6]							X							X							X						X	X	X
NPI-10[6]							X							X							X						X		X

Study Week	80	84	88	92	96	100	104	108	112	116	120	124	128	132	136	140	144	148	152	156	160	164	168	172	176	180	182 (EoT)	UV for a change in AD medication	FU /ET
Study Day	561 ±5	589 ± 5	617 ± 5	645 ± 5	673 ± 5	701 ± 5	729 ± 5	757 ± 5	785 ± 5	813 ± 5	841 ± 5	869 ± 5	897 ± 5	925 ± 5	953± 5	981± 5	1009 ±5	1037 ±5	1065 ±5	1093 ±5	1121 ± 5	1149 ± 5	1177 ± 5	1205 ± 5	1233 ± 5	1261 ±5	1275± 5		1387±7
EQ-5D (IR-S)[6]							X							X							X						X		X
EQ-5D, (IR-I)[6]							X							X							X						X		X
Caregiver Burden Measures[6]							X							X							X						X		X
C-SSRS														X													X		X
AE Reporting	Monitor and record continuously throughout the study																												
Concomitant Therapy and procedures	Monitor and record continuously throughout the study																												
SAE Reporting	Monitor and record continuously throughout the study																												

AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); CDR = Clinical Dementia Rating; CSF: cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) = EQ-5D, subject self-reported; EOT = End of Treatment; ET = Early Termination; FU = Follow-up; LTE = long-term extension; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; PET = positron emission tomography; SAE = serious adverse event; UV = unscheduled visit.

[1] Subjects who were in the placebo group during the placebo-controlled period will be randomized to aducanumab high and low dose (1:1 ratio).
[2] Required for women of childbearing potential only (Section 15.5).
[3] Sample will be collected prior to infusion (where applicable).
[4] Enrolled subjects who consented to CSF collection during the placebo-controlled period will have the option to consent to CSF collection during the LTE.
[5] Only for subjects who participate in the PET cohort.
[6] To be performed 14 ±7 days after the indicated dosing visit (i.e., Weeks 106, 134 and 162) and at Week 182.

Table 4: Brain MRI, Aria Management, and Follow-Up Phone Call Schedule During the Long-Term Extension

	Long-Term Extension													FU/ET
Study Week	**82**	**86**	**90**	**94**	**98**	**102**	**106**	**110**	**122**	**134**	**158**	**182**	**Unscheduled visit for ARIA[1]**	**198**
Study Day	**575±5**	**603±5**	**631±3**	**659±5**	**687±5**	**715±5**	**743±5**	**771±5**	**855±5**	**937±5**	**1107±5**	**1247±5**		**1387 ±7**
Follow-up Phone Call	X	X	X	X	X	X	X	X						
Brain MRI[2]				X		X		X	X	X	X	X	X	X
MOCA													X	

ARIA = amyloid related imaging abnormalities; ET = Early Termination; FU = follow-up; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging

[1] Details on ARIA management are in Section 7.2.

[2] Arterial-spin labeling MRI and task-free functional MRI will be performed only at a subset of sites.

4.3. Additional Information

4.3.1. Site Personnel

For each subject, the Principal Investigator (PI) of the site will designate the following investigational site personnel:

- Two independent rating health care professionals (the PI cannot serve as a rating health care professional); one who is responsible for administering the Clinical Dementia Rating (CDR) and a second who will administer the Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13], Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) (ADCS-ADL-MCI), and the Mini-Mental State Examination (MMSE)

  The rating health care professionals must not be involved with any other aspect of subject care and management and must remain blinded to adverse events (AEs), concomitant therapy, laboratory data, imaging data or any other data that have the potential of revealing the treatment assignment.

  To ensure consistency across sites, rating health care professionals must complete the standardized study-specific qualification process on clinical efficacy assessment scoring prior to administration of the specific assessment at their site. All sites should attempt to maintain the same rating health care professional throughout the study for specific assessments. Each subject should have the same rating health care professional perform the subject's specific rating assessment throughout the study. If a rating health care professional has to be replaced, the new rating health care professional must undergo the study-specific qualification process prior to administration of the assessment.

- A treating health care professional (the PI may serve as a treating health care professional) who is responsible for the following:
  - Administration of Montreal Cognitive Assessment (MOCA) at Day 1 and during management of ARIA cases.
  - Management of the routine neurological care of the subject.
  - Assessment (including assignment of causality) and treatment of AEs.
  - Review of selected hematology and blood chemistry results from the central laboratory to assess if the subject's study treatment should be temporarily withheld or permanently discontinued according to the criteria detailed in Section 10.1.

  Hematology and blood chemistry data will be sent to the investigational sites to aid in management of the subject. As with other laboratory and clinical information, these data should NOT be reviewed by the rating health care professionals.

The roles of independent raters and treating health care professional are NOT interchangeable at the subject level. In addition, the 2 independent raters are not interchangeable at the subject

level. If a rater has administered the CDR to a subject they may not administer the other neurocognitive assessments to that subject at any point during the study.

- An unblinded pharmacist (or authorized designee) will be responsible for the storage, distribution, preparation and accountability of study treatment. The unblinded pharmacist will also be responsible for maintaining the unblinded pharmacy record separate from the main study file in order to support the study blind.

5. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 50% to 75% of all cases. Alzheimer's Disease International estimates that as of 2013, there were 44.4 million people living with dementia worldwide and that this figure will increase to 135.5 million by 2050 [Alzheimer's Disease International 2014].

Clinically, AD is a progressive neurodegenerative disorder characterized by an insidious and unrelenting decline in cognition and behavioral disturbances that result in the person's inability to perform usual activities of daily living [Jack 2013].

Pathologically, AD is defined by the presence in the brain of extracellular neuritic plaques containing β-amyloid (Aβ) peptide and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau proteins. The pathogenesis of these plaques and tangles and how they contribute to the clinical syndrome remain to be fully elucidated, but the leading hypothesis — the "amyloid cascade"— proposes that the driving force behind the disease process is the accumulation of Aβ resulting from an imbalance between Aβ production and Aβ clearance in the brain [Hardy and Selkoe 2002].

The current view of AD, the disease process and its clinical manifestations, is that it manifests along a continuum rather than having categorical stages. Evidence suggests the pathophysiological changes begin years before clinical onset and as the disease progresses cognitive impairments, behavioral changes, and functional disability manifest [Jack 2013]. Revised criteria for the clinical diagnosis of AD were published by the National Institute on Aging (NIA) and the Alzheimer's Association (AA) [Albert 2011; McKhann 2011; Sperling 2011] and the International Working Group (IWG) [Dubois 2010; Dubois 2014], and a group that included members from both NIA-AA and IWG published recommendations to harmonize the criteria [Morris 2014]. These criteria base the diagnosis of AD on both clinical and biological elements, recognizing the existence of a nonclinical stage of the disease by accepting AD diagnoses prior to signs of dementia using AD biomarkers.

The scientific community has shifted its focus to target patients in the earlier course of the disease continuum with the belief that those patients are more likely to benefit from anti-amyloid therapy. Supporting this hypothesis are results from solanezumab and crenezumab studies that have shown a trend in slowing cognitive decline in mild but not moderate AD [Doody 2014; Fagan 2014].

There are currently no therapies that modify the course of AD, but several potential disease-modifying drug candidates are under investigation. These candidates include small molecules and immunotherapy (active and passive) that target the Aβ pathway and aim to provide therapeutic benefit by reducing either soluble or insoluble forms of Aβ in the brain and cerebrospinal fluid (CSF). Aducanumab is a human monoclonal antibody that recognizes aggregated forms of Aβ, including soluble Aβ oligomers and deposited fibrillar Aβ. Earlier publications have reported on results that demonstrated in the brain of an animal model of AD that both soluble oligomers and amyloid plaques are neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008] and clearance of amyloid plaques could lead to normalization of

calcium homeostasis and neuronal activity, as well as reduction of oxidative stress [Rozkalne 2009; Spires-Jones 2009]. Similarly, patients with AD who generated anti-Aβ antibodies after active immunization with aggregated Aβ(42) showed slower rates of decline of cognitive function and activities of daily living [Hock 2003].

5.1. Profile of Previous Experience with Aducanumab

5.1.1. Nonclinical Experience

Aducanumab is a unique human, anti-Aβ monoclonal antibody identified and derived from B lymphocytes using the reverse translational medicine approach. Using this technique, immune repertoires obtained from cohorts of healthy elderly human donors with excellent cognitive performance or with impaired but stable courses were screened for memory B cells against aggregated Aβ.

In vitro studies have demonstrated that aducanumab and its analogs are highly selective for soluble oligomeric and insoluble fibrillar forms of Aβ relative to soluble low-molecular-weight forms of Aβ. In vivo pharmacology studies indicated that a murine immunoglobulin (Ig) G2a chimeric version of the antibody (ch12F6A) with similar properties significantly reduced amyloid plaque burden in the brains of aged Tg2576 mice, a mouse model of AD, through a microglia-mediated phagocytic mechanism. These data suggest aducanumab could provide benefit by reducing plaque burden.

The toxicokinetic profile of aducanumab was evaluated in Tg2576 mice in 13-week and 6-month studies and in cynomolgus monkeys in a 4-week study. Of the 2 species, the Tg2576 mouse is considered the primary pharmacologically relevant species given that these mice accumulate amyloid plaques in the cerebral parenchyma and vasculature. In addition to the standard histopathological evaluation in mice, Perls' staining of hemosiderin (a breakdown product of hemoglobin) was performed to quantify microhemorrhage. Microhemorrhage has been observed both as a background finding in transgenic mouse models of AD [Winkler 2001], including Tg2576 mice [Kumar-Singh 2005], and as a drug-related finding in transgenic mice treated with some anti-Aβ antibodies [Pfeifer 2002; Racke 2005; Wilcock and Colton 2009].

Findings consistent with amyloid plaques and vascular amyloid were identified in the brain sections of animals in all groups, including the control group, as expected with this model. In both studies, repeated administration of ch12F6A or aducanumab was well tolerated with no treatment-related deaths observed during the dosing period. In the 13-week toxicology study, meningeal/cerebral vascular inflammation and/or vascular thickening were observed in mice dosed with ch12F6A ≥70 mg/ kg compared with the control group. In the 6-month study, although slight differences were observed between ch12F6A-treated groups and the control group, animals treated with aducanumab were comparable to the control animals. The evaluation of microhemorrhage, characterized by quantification of hemosiderin in Perls stained brain sections of each main study and recovery animal, demonstrated no significant increase in scores with ch12F6A or aducanumab treatment in either study. The incidence and severity of hemorrhage or cerebral vascular inflammation were comparable in the 13-week and 6-month mouse studies.

See the Investigator's Brochure (IB) for detailed information on nonclinical studies.

5.1.2. Clinical Experience

Aducanumab has been evaluated in one completed single ascending dose study (221AD101) and one ongoing multiple ascending dose study (221AD103):

- Study 221AD101 was a Phase 1, randomized, double-blind, placebo-controlled, study of aducanumab in subjects with mild or moderate AD.

  The primary objective was to evaluate the safety and tolerability of a range of aducanumab doses (0.3 to 60 mg/kg) when administered as single intravenous (IV) infusions. The secondary objectives were to assess the pharmacokinetic (PK) and immunogenicity of aducanumab after single-dose administration.

  A single dose of aducanumab up to 30 mg/kg was demonstrated to be well tolerated. Dose-limiting ARIA (2 subjects with ARIA-E [edema] and 1 subject with ARIA-E and ARIA-H [microhemorrhage]) was observed in the 60 mg/kg dose group resulting in termination of further dosing in that cohort; no cases of ARIA were observed at single doses below 60 mg/kg. The PK profile was dose linear.

- Study 221AD103 is a randomized, double-blind, placebo-controlled multiple dose study of aducanumab in subjects with prodromal or mild AD who are amyloid positive. The study comprises a placebo-controlled period with subjects receiving monthly doses of aducanumab (fixed doses of 1, 3, 6, or 10 mg/kg, or titration up to 6 mg/kg) or placebo for a year followed by a dose-blind long-term extension (LTE) period with subjects receiving monthly doses of aducanumab.

  The primary objective of the study is to evaluate the safety and tolerability of multiple doses of aducanumab administered monthly as single IV infusions. The secondary objectives are to assess the effect of aducanumab on cerebral amyloid plaque content as measured by ^{18}F-florbetapir positron emission tomography (PET), and to evaluate the PK and immunogenicity of aducanumab after multiple-dose administration. Exploratory objectives include assessment of the effect of aducanumab on the clinical progression of AD as measured by CDR- sum of boxes (SB) and MMSE.

  To date, ARIA has been the most frequent AE reported in the study. ARIA-E was radiographically monitored by magnetic resonance imaging (MRI) and typically observed early in treatment (between 2 to 5 doses). In most cases, ARIA-E resolved 4 to 12 weeks after onset and ARIA-H was typically stable 2 to 4 weeks after onset. Incidence of ARIA has been observed to be both dose and Apolipoprotein E4 (ApoE ε4) carriage-dependent, especially at the highest doses (refer to the IB for details on events of ARIA).

  Protocol-defined interim analyses have demonstrated a dose- and time-dependent reduction of brain amyloid burden after 6 months of dosing (Week 26), with statistical significance achieved in the 3, 6, and 10 mg/kg groups compared with placebo, and after 1 year of dosing (Week 54), with statistical significance achieved in the 3 and 10 mg/kg groups compared with placebo (6 mg/kg data not yet

available). The results demonstrate target engagement (amyloid plaques) and a pharmacodynamic effect (dose-dependent amyloid reduction). In addition results from the interim analyses showed an effect at 1 year on the exploratory endpoints CDR-SB and MMSE, suggesting a reduction in the progression of clinical impairment for aducanumab-treated versus placebo-treated subjects. At Week 54, adjusted mean change (increase) from baseline in CDR-SB score was smaller for both the 3 and 10 mg/kg groups compared with placebo, with statistical significance achieved in the 10 mg/kg group (6 mg/kg data not yet available). At Week 52, adjusted mean changes (decreases) in MMSE score from baseline were statistically significant in the 3 and 10 mg/kg groups (Week 54 6 mg/kg data not yet available). Refer to the IB for details on interim analyses results.

5.2. Study Rationale

The purpose of this study is to assess the efficacy and safety of aducanumab compared with placebo in subjects with early AD including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD. Aducanumab is a human monoclonal antibody that recognizes aggregated forms of Aβ, including soluble Aβ oligomers and deposited fibrillar Aβ. Earlier publications have demonstrated that both soluble oligomers and amyloid plaques are neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008] and clearance of amyloid plaques could lead to normalization of calcium homeostasis and neuronal activity, as well as reduction of oxidative stress in the brain of an animal model of AD [Rozkalne 2009; Spires-Jones 2009]. For this reason, treatment with aducanumab is expected to slow progression of AD, while preserving global function longer, when compared with untreated subjects.

Interim analyses of the ongoing multiple dose study (Study 221AD103) have demonstrated target engagement, a PD effect on amyloid reduction, and an effect on CDR-SB and MMSE suggestive of a reduction in the progression of clinical impairment for aducanumab-treated subjects. These results along with the observed safety and tolerability profile warrant the further Phase 3 investigation of aducanumab in a patient population spanning the early stages of the AD continuum.

5.3. Rationale for Dose and Schedule Selection

The dosing regimen selected for this study was based on the PK and PD relationship for removal of brain amyloid and effect on CDR-SB and MMSE observed in Study 221AD103 interim analyses and on safety, tolerability, and PK data from studies 221AD101 (complete) and 221AD103 (ongoing).

The dose- and time-dependent reduction of brain amyloid burden observed with aducanumab treatment was statistically significant at doses of 3, 6 and 10 mg/kg after 6 months of dosing and at 3 and 10 mg/kg after 12 months of dosing (6 mg/kg data not yet available). The effect on mean decrease from baseline in CDR-SB after 12 months of dosing was observed at both 3 and 10 mg/kg (6 mg/kg data not yet available), with statistical significance achieved at 10 mg/kg. The effect on mean decrease from baseline in MMSE score was statistically significant at 3 and 10 mg/kg. These data indicate that 3 mg/kg could be considered an acceptable dose for Phase 3

studies; however, given the dose-dependent nature of these observations, the use of higher doses (6 and 10 mg/kg) could offer greater benefit at acceptable risk.

ARIA has been identified as an event that may occur with anti-amyloid targeting drug candidates and is considered an event of special interest in the aducanumab program. To date, the incidence of ARIA has been observed to be both dose and ApoE ε4 carriage dependent, especially at the highest doses. In an effort to maximize the dose-dependent amyloid reduction and effect on CDR-SB and MMSE that have been observed with doses of 3 mg/kg and higher while maintaining ARIA incidence, severity, and related discontinuation rate within acceptable levels, a titration regimen will be explored. It has been suggested that the ARIA observed following treatment with amyloid targeting agents may be due, in part, to the initial large removal of amyloid and subsequent saturation of perivascular brain amyloid clearance mechanisms [Weller 2008]. Slow titration to the target dose is expected to result in slower initial amyloid removal, yet trigger alternative mechanisms of amyloid clearance including monoclonal antibody-dependent Fc-mediated microglial clearance [Ostrowitzki 2012] which would prevent saturation of amyloid clearance and subsequent ARIA during titration and once the target dose is reached. Since aducanumab-induced ARIA has been demonstrated to occur early during treatment, with most cases occurring within the first 5 doses, titration of aducanumab for up to 6 doses prior to reaching the target dose may result in reduction of ARIA incidence and severity.

Given the tolerability and apparent efficacy of aducanumab shown to date, the doses to be tested using a titration regimen are 3 and 6 mg/kg for ApoE ε4 carriers, and 6 and 10 mg/kg for ApoE ε4 non-carriers. Titration will start at 1 mg/kg and will escalate to 3, 6 and 10 mg/kg as detailed below.

5.3.1. Dosing Scheme

5.3.1.1. Placebo-Controlled Period

Doses will be administered approximately 4 weeks apart, over approximately 76 weeks (a total of 20 doses). Based upon their ApoE ε4 carrier status, subjects will be assigned to 1 of 3 treatment groups (450 subjects each) in a 1:1:1 ratio (aducanumab low dose: aducanumab high dose: placebo) as follows (Table 5 and Figure 1):

ApoE ε4 carrier

- Low dose (3 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg thereafter
- High dose (6 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 4 doses, and 6 mg/kg thereafter
- Placebo

  Saline infusion

ApoE ε4 non-carrier

- Low dose (6 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 4 doses, and 6 mg/kg thereafter

- High dose (10 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter

- Placebo

  Saline infusion

Table 5: Dosing Scheme for Aducanumab by Regimen

Dose (Month)		**1**	**2**	**3**	**4**	**5**	**6**	**7 to 20**
Regimen		**Dose (mg/kg)**						
ApoE ε4 (+)	**Low Dose**	1	1	3	3	3	3	3
	High Dose	1	1	3	3	3	3	6
	Placebo	saline						
ApoE ε4 (-)	**Low Dose**	1	1	3	3	3	3	6
	High Dose	1	1	3	3	6	6	10
	Placebo	saline						

5.3.2. Dosing Scheme Modification

An independent data monitoring committee (IDMC) will review unblinded safety data, including serious AEs (SAEs) and incident cases of ARIA, from all ongoing aducanumab studies (e.g., Studies 221AD103, 221AD104, 221AD301, and 221AD302) as described in the IDMC charter.

The dosing scheme can be modified in the following circumstances:

- Safety and tolerability of the high dose

  If any of the high doses proposed (10 mg/kg in ApoE ε4 non-carriers and 6 mg/kg in ApoE ε4 carriers) is deemed not acceptable, enrollment for the high dose group(s) will be terminated and subjects will not be replaced. Subjects who have already been randomized to the discontinued dose will be down-dosed to the next available dose according to their ApoE ε4 carrier status. Definition of low and high dose regimens will be revised as described in Section 16.

- Benefit of titration

  A titration schedule has been implemented in this Phase 3 study and in the ongoing multiple-dose Study 221AD103. If, based upon review of the data from

Study 221AD103, titration is not deemed beneficial, it will be eliminated, and subsequently enrolled subjects who are ApoE ε4 carriers will receive a fixed dose of 3 or 6 mg/kg and non-carriers will receive 6 or 10 mg/kg.

5.3.3. Long-Term Extension

Subjects who received aducanumab in the placebo-controlled period and who enter the LTE will continue to receive the same dose of aducanumab that they were on at the end of the placebo-controlled period. Subjects who receive placebo during the placebo-controlled period and who enter the LTE period will be assigned to 1 of 2 treatment groups, based upon their ApoE ε4 carrier status, in a 1:1 ratio (aducanumab low dose: aducanumab high dose). Subjects will be dosed using the same regimen described for the placebo-controlled period (see Table 5 and Figure 1).

Any modifications to the dosing scheme (i.e. termination of high dose groups and replacement of titration with fixed dosing, as described in Section 5.3.2) will also be implemented in the LTE.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

The primary objective of the study is to evaluate the efficacy of monthly doses of aducanumab in slowing cognitive and functional impairment as measured by changes in the CDR-SB score as compared with placebo in subjects with early AD.

The primary endpoint that relates to this objective is change from baseline in CDR-SB score at Week 78.

6.2. Secondary Objectives and Endpoints

A secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by the MMSE.

- The endpoint that relates to this objective is change from baseline in MMSE score at Week 78.

Another secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by ADAS-Cog 13.

- The endpoint that relates to this objective is change from baseline in ADAS-Cog 13 score at Week 78.

Another secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by ADCS-ADL-MCI.

- The endpoint that relates to this objective is change from baseline in ADCS-ADL-MCI score at Week 78.

6.3. Tertiary Objectives and Endpoints

6.3.1. Tertiary Objectives

Safety and Tolerability

- To assess the safety and tolerability of monthly doses of aducanumab.
- To assess the immunogenicity of aducanumab.

Biomarker

- To assess the effect of aducanumab on cerebral amyloid plaque content as measured by amyloid PET imaging (in a subset of approximately 400 subjects).
- To assess the effect of aducanumab on various morphometric measures in certain brain areas as measured by MRI.
- To assess the effect of aducanumab on functional connectivity by task free functional (tf)-fMRI (where available).

- To assess the effect of aducanumab on cerebral blood flow by arterial spin labeling (ASL)-MRI (where available).
- To assess the effect of aducanumab on disease-related biomarkers in CSF which will include, but are not limited to, amyloid and tau proteins (in a subset of subjects).
- To assess the effect of aducanumab on disease-related biomarkers in blood which may include, but are not limited to, amyloid and tau proteins.

Efficacy

- To assess the effect of aducanumab on behavior as measured by the Neuropsychiatric Inventory (NPI-10).
- To assess the effect of aducanumab on patient health status, measured by EuroQol health status measures (EQ-5D [informant-rated and patient self-reported]).
- To assess the effect of aducanumab on the informant/study partner's own health status, measured by the EQ-5D.
- To assess the effect of aducanumab on patient self-reported cognitive function, measured by the modified Perceived Deficits Questionnaire-20 (mPDQ-20) [Lenderking 2014].
- To assess the effect of aducanumab on caregiver burden measures.
- To assess the correlation between primary endpoints and key biomarker endpoints.

Pharmacokinetics

- To explore the potential relationships between PK or exposure and response (e.g., clinical and biomarker endpoints) including covariate analysis.
- To explore the potential effect of co-medications on the PK of aducanumab using population PK.

6.3.2. Tertiary Endpoints

Safety and Tolerability:

- Incidence of all AEs and SAEs.
- Brain MRI findings including incidence of ARIA-E and ARIA-H.
- Clinical laboratory shifts in reported values.
- Clinically significant changes in vital sign measurements and electrocardiograms (ECGs).
- Incidence of anti-aducanumab antibodies in serum.

Biomarkers:

- Change from baseline in amyloid PET signal at Week 26 (in a subset of subjects).

- Change from baseline in amyloid PET signal at Week 78 (in a subset of subjects).
- Change from baseline in whole brain volume, hippocampal volume, ventricular volume, and cortical gray matter volume measured by MRI over time.
- Change from baseline in functional connectivity as measured by tf-fMRI (where available) over time.
- Change from baseline in cerebral blood flow as measured by ASL-MRI (where available) over time.
- Change in disease-related biomarker levels in CSF, which will include, but are not limited to, amyloid or tau proteins at Week 78 (in a subset of subjects).
- Change in disease-related biomarker levels in blood, which may include, but are not limited to, amyloid or tau proteins at Week 24.
- Change in disease-related biomarker levels in blood, which may include, but are not limited to, amyloid or tau proteins at Week 78.

Efficacy

- Change from baseline in NPI-10 score at Week 78.
- Change from baseline in subject-self-reported EQ-5D index score at Week 78.
- Change from baseline in informant-rated subject EQ-5D index score at Week 78.
- Change from baseline in informant/care partner's own EQ-5D index-score at Week 78.
- Change from baseline in mPDQ-20 at Week 78.
- Changes in caregiver burden questionnaire over time.
- Correlation between clinical and biomarker endpoints over time.

Pharmacokinetics

- Serum concentrations of aducanumab, population PK parameters of aducanumab including but not limited to clearance and volumes of central and peripheral compartments.

6.4. Long Term Extension Objectives and Endpoints

6.4.1. Objectives

- To evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD.
- To evaluate the long-term efficacy of aducanumab treatment as measured by clinical, radiological, and additional assessments reported by the subject and informant/care partner.

6.4.2. Endpoints

- The incidence of AEs and/SAEs; brain MRI findings (including the incidence of ARIA-E and ARIA-H); and the incidence of anti-aducanumab antibodies in serum over the placebo-controlled and LTE periods of the study.
- Change in the following measures over the placebo-controlled and LTE periods of the study:
  - CDR-SB score.
  - MMSE score.
  - ADAS-Cog 13 score.
  - ADCS-ADL-MCI score.
  - Amyloid PET signal (in a subset of subjects).
  - Whole brain volume, hippocampal volume, ventricular volume, and cortical gray matter volume measured by MRI.
  - Functional connectivity as measured by tf-fMRI (where available).
  - Cerebral blood flow as measured by ASL-MRI (where available).
  - Disease-related biomarker levels in CSF which will include, but are not limited to, amyloid and tau proteins (in a subset of subjects).
  - Disease-related biomarker levels in blood which may include, but are not limited to, amyloid and tau proteins.
  - NPI-10 total score.
  - Informant-rated EQ-5D index score.
  - Informant/care partner’s own self-reported EQ-5D index score.
  - Caregiver burden measures.

7. STUDY DESIGN

7.1. Study Overview

Study 221AD301 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects with early AD, including MCI due to AD and a subset of mild AD, followed by an optional 24-month dose-blind LTE study. Approximately 1350 subjects will be enrolled across approximately 150 centers globally. The primary study objective is to evaluate the efficacy of monthly doses of aducanumab on the CDR-SB relative to placebo. Secondary objectives include assessment of the effect of monthly doses of aducanumab on clinical progression as compared to placebo. The safety of monthly doses of aducanumab will also be evaluated.

Subjects will receive infusions of aducanumab or placebo approximately every 4 weeks for approximately 18 months (a total of 20 doses). Subjects will be randomized to receive aducanumab low dose : aducanumab high dose : placebo in a 1:1:1 ratio. The randomization will be stratified by site and ApoE ε4 status (carrier or non-carrier). Subject enrollment will be monitored so that approximately 60% to 70% ApoE ε4 carriers are enrolled. Enrollment will also be monitored, via interactive response technology (IRT), such that subjects with mild AD represent a small percentage of the total enrolled in the trial.

At the end of the double-blind, placebo-controlled treatment period, subjects who meet the extension entry criteria may enter a 24-month long-term safety and efficacy extension period, with all subjects receiving aducanumab approximately every 4 weeks (a total of 26 doses).

The total duration of study participation for each subject only participating in the placebo-controlled period of the study will be up to approximately 102 weeks, including a series of screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, and a safety follow-up period of approximately 18 weeks after the final dose. The total duration of study participation for each subject participating in the placebo-controlled period and the LTE will be up to approximately 206 weeks, including a series of screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, a 4-week follow-up period, a 100-week aducanumab dose-blind treatment period, and a safety follow-up period of approximately 18 weeks after the final dose. The follow-up period of 18 weeks is based on an estimated mean elimination half-life in humans of 16 to 24 days (mean approximately 20 days, based on results from the single ascending dose study [Study 221AD101]) and anticipated brain concentrations of aducanumab of less than one-third the EC_{50} (inhibitory concentration at 50% of the maximum observed biologic effect) for binding fibrillar amyloid at 8 weeks after the last dose.

During the placebo-controlled period, ApoE ε4 carriers will receive placebo, aducanumab 3 mg/kg, or aducanumab 6 mg/kg whereas ApoE ε4 non-carriers will receive placebo, aducanumab 6 mg/kg, or aducanumab 10 mg/kg. Aducanumab will be titrated for up to 6 doses prior to reaching the target dose as shown in Table 5 and Figure 1. Subjects who received aducanumab in the placebo-controlled period and who enter the LTE period will receive the

same dose of aducanumab that they received at the end of the placebo-controlled period (up to 6 mg/kg and 10 mg/kg in ApoE ε4 carriers and non-carriers, respectively). Subjects who received placebo during the placebo-controlled period and who enter the LTE period will be assigned to treatment based upon their ApoE ε4 carrier status in a 1:1 ratio (aducanumab low dose: aducanumab high dose); aducanumab will be titrated for up to 6 doses prior to reaching the target dose following the same schedule described for the placebo-controlled period.

See Section 5.3.2 for details of dosing scheme modification.

Individual dose adjustments may also be implemented to subjects who develop ARIA. See Section 7.2.1.

Investigators, study site staff (except for the designated unblinded pharmacist/technician), and study subjects will be blinded to the subjects' randomized treatment assignment for the placebo-controlled period. During the LTE, investigators and subjects will remain blinded to the treatment assignment in the placebo-controlled period and the aducanumab dose for the LTE.

7.2. Study Specifics

7.2.1. Dose Suspension, Modification or Termination for ARIA Events

Discontinuation of Dosing for a Given Subject

The central MRI reading center will report incident cases of ARIA-E and ARIA-H to both the Sponsor and the Principal Investigator within a specified time after observing the finding on MRI per the imaging manual procedures. All cases of ARIA will be reviewed by the Sponsor and the Principal Investigator; decisions on dosing continuation, interruption, or discontinuation will be based on clinical symptoms, and the MRI information provided by the central reader. IDMC notification rules will be outlined in the IDMC charter. Disposition of ARIA-E cases is presented in Table 6 , ARIA-H (microhemorrhage) in Table 7, and ARIA-H (superficial siderosis) in Table 8.

7.2.1.1. Disposition of ARIA-E cases

Table 6: Disposition of ARIA-E Cases

<table>
<tr><th rowspan="2">Clinical Symptom Severity</th><th colspan="3">ARIA-E Severity on MRI</th></tr>
<tr><th>Mild</th><th>Moderate</th><th>Severe</th></tr>
<tr><td>Asymptomatic</td><td>Continue dosing at current dose and schedule</td><td>Suspend dosing; once ARIA-E resolves the subject may resume dosing at next lower dose</td><td>Suspend dosing; once ARIA-E resolves, the subject may resume dosing at next lower dose</td></tr>
<tr><td>Mild</td><td colspan="3" rowspan="2">Suspend dosing; once ARIA-E and clinical symptoms resolve, the subject may resume dosing at next lower dose</td></tr>
<tr><td>Moderate</td></tr>
<tr><td>Severe or Serious</td><td colspan="3">Discontinue Dosing</td></tr>
</table>

- Subjects who develop **mild ARIA-E, per central MRI reading, with no clinical symptoms** at any time during the study may continue in the study at their current

dose. Subjects should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. The Sponsor may require that the subjects discontinue dosing or continue dosing at a lower dose level based on review of safety and MRI data.

- Subjects who develop **moderate or severe ARIA-E, per central MRI reading, with no clinical symptoms** at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. If the ARIA-E has resolved and the subjects remain asymptomati**c**, the subjects may resume treatment but at the next lower dose level. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment. Guidance for dose reduction is presented in Section 7.2.1.4.
- Subjects who develop **mild, moderate, or severe ARIA-E, as per central MRI reading, accompanied by mild or moderate clinical symptoms** at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. If the ARIA-E has resolved and the clinical symptoms have resolved, the subject may resume treatment but at the next lower dose level. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment. Guidance for dose reduction is presented in Section 7.2.1.4.
- Subjects who develop **mild, moderate, or severe ARIA-E, as per central MRI reading, accompanied by severe or serious clinical symptoms** at any time during the study will permanently discontinue treatment. Subjects should complete all scheduled clinic visits for assessments and in addition, have an unscheduled visit for an MRI and MOCA approximately every 4 weeks until the ARIA-E has resolved per centrally read MRI.

7.2.1.2. Disposition of ARIA-H cases

Table 7: Disposition of ARIA-H (microhemorrhage) Cases

<table>
<tr><th rowspan="2">Clinical Symptom Severity</th><th colspan="3">New Incident Microhemorrhages Within 12 Weeks</th></tr>
<tr><th>≥ 1 and ≤ 4</th><th>≥ 5 and ≤ 9</th><th>≥ 10</th></tr>
<tr><td>Asymptomatic</td><td>Continue dosing at current dose and schedule</td><td>Suspend dosing; once ARIA-H is stable the subject may resume dosing at next lower dose</td><td rowspan="4">Discontinue dosing</td></tr>
<tr><td>Mild</td><td colspan="2" rowspan="2">Suspend dosing; once ARIA-H stabilizes and clinical symptoms resolve, the subject may resume dosing at next lower dose</td></tr>
<tr><td>Moderate</td></tr>
<tr><td>Severe or Serious</td><td colspan="2">Discontinue dosing</td></tr>
</table>

7.2.1.2.1. Asymptomatic ARIA-H (microhemorrhage):

- Subjects who develop a **≥ 1 and ≤ 4 new incident microhemorrhage(s)** within 12 weeks at any time during the study may continue treatment at the current dose.
- Subjects who develop **≥ 5 and ≤ 9 new incident microhemorrhages** occurring within 12 weeks at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 2 weeks until the microhemorrhage is confirmed as stable per the centrally read MRI. A microhemorrhage is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks later. Once the microhemorrhage is deemed stable, subjects may resume treatment at the next lower dose. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment. Guidance for dose reduction is presented in Section 7.2.1.4.

Table 8: Disposition of ARIA-H (superficial siderosis) Cases

Clinical Symptom Severity	New Incident Areas of Superficial Siderosis Within 12 Weeks		
	1	2	> 2
Asymptomatic	Continue dosing at current dose and schedule	Suspend dosing; once ARIA-H is stable the subject may resume dosing at next lower dose	Discontinue dosing
Mild	Suspend dosing; once ARIA-H stabilizes and clinical symptoms resolve, the subject may resume dosing at next lower dose		
Moderate			
Severe or Serious	Discontinue dosing		

7.2.1.2.2. Asymptomatic ARIA-H (superficial siderosis):

- Subjects who develop a **single incident focal area of hemosiderosis** (**also referred to as superficial siderosis)** may continue treatment at the current dose, but must have an unscheduled visit for an MRI and MOCA approximately every 2 weeks until the superficial siderosis is confirmed as stable per the centrally read MRI. Superficial siderosis is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks later.
- Subjects who develop **2 focal areas of hemosiderosis (superficial siderosis)** occurring within 12 weeks at any time during the study will temporarily suspend treatment but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 2 weeks until the ARIA-H (superficial siderosis) is confirmed as stable per the centrally read MRI. Superficial siderosis is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks later. Once the superficial siderosis is deemed stable, the subjects may resume treatment at the next lower dose. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment. Guidance for dose reduction is presented in Section 7.2.1.4.

7.2.1.2.3. Symptomatic ARIA-H (microhemorrhage(s) or superficial siderosis):

- Subjects who develop **≤ 9 new incident microhemorrhages or ≤ 2 new focal area of superficial siderosis** within 12 weeks and mild or moderate clinical symptoms will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 2 weeks until the ARIA-H (microhemorrhage(s)) is confirmed as stable per the centrally read MRI. Microhemorrhage(s) are considered stable if they are unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks later. Once the ARIA-H is deemed stable and the clinical symptoms have resolved, the subjects may resume treatment but at the next lower dose level. Only subjects who have not missed more than 4 consecutive doses

will be allowed to resume treatment. Guidance for dose reduction is presented in Section 7.2.1.4.

- Subjects who experience **severe clinical symptoms associated with ARIA-H (microhemorrhage(s) or superficial siderosis)** will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and in addition, have an unscheduled visit for an MRI and MOCA approximately every 2 weeks until the ARIA-H microhemorrhage(s) or superficial siderosis is confirmed as stable per centrally read MRI.

7.2.1.2.4. ARIA-H (microhemorrhage(s) or superficial siderosis) requiring permanent discontinuation:

- Subjects who develop **≥ 10 new incident microhemorrhages or > 2 new focal areas of superficial siderosis** within 12 weeks regardless of clinical severity will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 2 weeks until the ARIA-H microhemorrhage(s) or superficial siderosis is confirmed as stable per central read MRI.

7.2.1.3. Disposition of Coincident ARIA-H and ARIA-E Cases:

Subjects who develop ARIA-H coincident with ARIA-E at any time during the study will follow ARIA-E guidelines. Prior to resuming treatment, where applicable, ARIA-E must resolve, ARIA-H be deemed stable, and the subject must be asymptomatic.

7.2.1.4. Dose Reduction for Subjects Developing ARIA:

Dose reduction guidance is presented in the Table 9 below. If further dose reduction is needed, the next lower dose level will be used. If more than 2 dose reductions are needed, Sponsor approval will be required prior to treatment continuation.

Table 9: Dose Reduction for Subjects Experiencing ARIA, Who Resume Treatment After Suspension

Current Dose	Resuming Dose
10 mg/kg	6 mg/kg
6 mg/kg	3 mg/kg
3 mg/kg	1 mg/kg
1 mg/kg	Placebo
Placebo	Placebo

ARIA = amyloid related imaging abnormality
Current dose refers to the dose that the subject was receiving before ARIA was detected

Subjects who develop ARIA during the placebo-controlled period but continue or resume treatment at an active dose are eligible to enter the LTE and will receive the lowest dose that they

have tolerated during the placebo-controlled period. A subject who is switched to placebo but remains in the study may be titrated to aducanumab 1 mg/kg during the LTE.

7.2.2. Infusion Interruption

If any mild or moderate infusion-related reactions (e.g., headache, chills/rigors, and nausea/vomiting) occur during an infusion, the infusion should be slowed or interrupted and supportive treatment should be instituted at the discretion of the Investigator. After resolution of symptoms, if the infusion had been slowed, the original infusion rate may be resumed; if the infusion had been interrupted, the infusion may be restarted at a rate that does not exceed the original infusion rate. An infusion must be discontinued if not completed within 3 hours.

Refer to the Directions for Handling and Administration [DHA] for infusion rate information.

If a severe infusion-related reaction occurs during an infusion, or an allergic reaction such as urticaria or anaphylaxis occurs, the subject should be discontinued from study treatment but may remain in the study. The subject must be appropriately treated in accordance with local practice.

Severity of events is described in Section 15.2.3.

7.3. Overall Study Duration and Follow-Up

The study period will consist of screening, treatment, and follow-up.

The double-blind, placebo-controlled period of the study will consist of an 8-week screening period, a 76-week treatment period, and a safety follow-up period of 18 weeks after the final dose.

Subjects will have approximately 33 scheduled clinic visits during the placebo-controlled period, and up to 8 telephone safety follow-up contacts, as follows:

- Screening Visits no more than 60 days before the first dose of study treatment on Day 1 (visits will be conducted on multiple days).
- 20 outpatient dosing visits.
- 8 telephone safety follow-up contacts approximately 2 weeks after each of the first 8 doses.
- 3 visits for clinical assessments.
- 1 visit for CSF biomarkers (optional).
- 2 visits for amyloid PET scan (in a subset of subjects).
- 6 visits for brain MRI.
- 1 follow-up safety visit at Week 94 (only for subjects not entering the LTE).

Subjects who meet the LTE inclusion and exclusion criteria will be eligible to enter the LTE. Subjects who enter the LTE will have approximately 40 additional planned clinic visits, and up to 8 telephone safety follow-up contacts, as follows:

- 26 outpatient dosing visits.

- 8 telephone safety follow-up contacts approximately 2 weeks after each of the first 8 doses.
- 4 visits for clinical assessments.
- 2 visits for CSF biomarkers (optional).
- 2 visit for amyloid PET scan (in a subset of subjects).
- 7 visits for brain MRI.
- 1 follow-up safety visit.

Subjects who have a change in AD medication (other than study treatment) during the placebo-controlled or LTE period should have an unscheduled visit; all clinical assessments for the primary and secondary endpoints should be performed prior to the change in medication.

Subjects who experience ARIA during the placebo-controlled or LTE period should have unscheduled visits as per the guidelines in Section 7.2.1.

7.3.1. Screening

During the Screening Visit, under a separate initial consent process, subjects can complete the neurocognitive scales (CDR, MMSE, and the Repeatable Battery for Assessment of Neuropsychological Status [RBANS]). This initial neurocognitive screening is intended to reduce the burden on subjects and sites by avoiding unnecessary testing if subjects do not meet key inclusion criteria. If the subject meets inclusion criteria for these 3 scales, then the full consent process must be completed prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process, which would allow the administration of all screening assessments.

The neurocognitive assessments that have exclusion cut points (CDR, MMSE and RBANS) must be performed at Screening Visit 1. The ADAS-Cog 13, ADCS-ADL-MCI and NPI-10 will be performed at Screening Visit 2 within 14 days after Visit 1 and must NOT be performed on the same day as the CDR, MMSE and RBANS. All other cognitive assessments as well as CSF collection may be performed at any time during screening after eligibility is confirmed during Screening Visit 1. The MRI at Screening Visit 2 should be done only after the subject eligibility based on clinical and laboratory criteria is confirmed during Screening Visit 1. The PET scan at Screening Visit 3 should be completed only after the MRI inclusion criterion is met.

Subject eligibility for the study will be determined no more than 60 days prior to study entry. Subjects who fail screening will be permitted to be rescreened once at the Sponsor’s discretion. Subjects who fail screening due to PET, MMSE, CDR, hepatitis B or C results, or abnormal MRI findings will not be allowed to re-screen.

7.3.2. Treatment

Eligible subjects will report to the study site to receive study treatment every 4 weeks for 76 weeks (20 doses). All subjects who meet the LTE inclusion and exclusion criteria will be eligible to enter the LTE and will receive study treatment every 4 weeks for an additional 100

weeks (26 doses), with the first dose administered approximately 4 weeks after the final dose in the placebo-controlled period of the study.

7.3.3. Follow-Up

All subjects participating in the placebo-controlled period are to return to the study site approximately 2 weeks after the final dose for clinical assessments.

Subjects participating in the placebo-controlled period and not entering the LTE are to return to the study site for a follow-up visit at Week 94 (18 weeks after the last dose). The final study visit for these subjects will be Week 94.

Subjects who participate in the LTE are to return to the study site to receive their first LTE dose approximately 4 weeks after their last dose in the placebo-controlled period of the study. A follow-up visit will occur at Week 198 (18 weeks after the last LTE dose). The final study visit for subjects participating in the LTE will be Week 198.

7.4. Study Stopping Rules

Biogen may terminate this study at any time, after informing Investigators. Biogen (or designee) will notify Investigators when the study is to be placed on hold, completed, or terminated.

Dosing may be terminated by the Sponsor at the recommendation of the IDMC, based exclusively on safety and tolerability data or following the futility analysis, or at the discretion of the Sponsor; therefore there are no study-specific stopping rules defined in this protocol.

7.5. End of Study

The end of study is last subject, last visit.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at Screening or at the time point specified in the individual eligibility criterion listed:

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.
2. Aged 50 to 85 years old, inclusive, at the time of informed consent.
3. All women of childbearing potential and all men must practice effective contraception during the study and for 24 weeks after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 15.5.
4. Must have at least 6 years of education or work experience to exclude mental deficits other than MCI or mild AD.
5. Must have a positive amyloid PET scan. Previously obtained PET scan (within 12 months of screening) is permissible for subjects not participating in the PET cohort. Previous PET scan images must be submitted to the central imaging vendor to confirm study inclusion criteria are met.
6. Must meet all of the following clinical criteria for MCI due to AD or mild AD according to NIA-AA criteria [Albert 2011; McKhann 2011], and must have:
   - A CDR-Global Score of 0.5.
   - An RBANS score of 85 or lower indicative of objective cognitive impairment.
   - An MMSE score between 24 and 30 (inclusive).
7. Apart from a clinical diagnosis of early AD, the subject must be in good health as determined by the Investigator, based on medical history and screening assessments.
8. Must consent to apolipoprotein E (Apo E) genotyping.
9. Has one informant/care partner who, in the Investigator's judgment, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally be available by phone to provide information to the Investigator and study staff about the subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study, and the use of the same informant/care partner for the duration of the study is encouraged.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening, or at the time point specified in the individual criterion listed:

Medical History

1. Any uncontrolled medical or neurological/neurodegenerative condition (other than AD) that, in the opinion of the Investigator, might be a contributing cause of the subject's cognitive impairment (e.g., substance abuse, vitamin B_{12} deficiency, abnormal thyroid function, stroke or other cerebrovascular condition, lewy body dementia, fronto-temporal dementia, head trauma)..
2. Clinically significant psychiatric illness (e.g., uncontrolled major depression, schizophrenia, bipolar affective disorder) within 6 months prior to Screening
3. Transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year prior to Screening.
4. Brain MRI performed at Screening (per centrally read MRI) that shows evidence of any of the following:
   - Acute or sub-acute hemorrhage.
   - Prior macrohemorrhage (defined as >1 cm in diameter on T2* sequence) unless it can be documented that the finding is not due to an underlying structural or vascular abnormality (i.e., finding does not suggest subject is at risk of recurrent hemorrhage).
   - Greater than 4 microhemorrhages (defined as ≤1 cm in diameter on T2* sequence).
   - Cortical infarct (defined as > 1.5 cm in diameter).
   - >1 lacunar infarct (defined as ≤ 1.5 cm in diameter).
   - Superficial siderosis.
   - History of diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scale [Wahlund 2001].
   - Any finding that, in the opinion of the Investigator, might be a contributing cause of subject's dementia, might pose a risk to the subject, or might prevent a satisfactory MRI assessment for safety monitoring.
5. History of bleeding disorder or predisposing conditions, blood clotting or clinically significant abnormal results on coagulation profile at Screening, as determined by the Investigator.
6. Poorly controlled diabetes mellitus as defined (according to the National Glycohemoglobin Standardization Program) by a glycosylated hemoglobin (HbA_{1c}) value of ≥ 7%.

7. History of unstable angina, myocardial infarction, chronic heart failure (New York Heart Association Class III or IV), or clinically significant conduction abnormalities (e.g., unstable atrial fibrillation) within 1 year prior to Screening.
8. Clinically significant 12-lead ECG abnormalities, as determined by the Investigator.
9. Uncontrolled hypertension defined as: average of 3 systolic blood pressure [SBP]/diastolic blood pressure [DBP] readings > 165/100 mmHg at Screening (blood pressure measurements exceeding these limits may be repeated as warranted by the Investigator, but values must be within the specified limits for the subject to be eligible for the study), or persistent SBP/DBP readings > 180/100 mmHg 3 months prior to randomization (Day 1) that in the opinion of the Investigator are indicative of chronic uncontrolled hypertension.
10. History of malignancy or carcinoma. The following exceptions may be made after discussion with the Sponsor:
    - Subjects with cancers in remission more than 5 years prior to Screening.
    - Subjects with a history of excised or treated basal cell or squamous carcinoma.
    - Subjects with prostate cancer in situ.
11. History of seizure within 10 years prior to Screening.
12. Indication of impaired liver function as shown by an abnormal liver function profile at Screening (e.g., repeated values of aspartate aminotransferase [AST] and alanine aminotransferase [ALT] $\geq 2 \times$ the upper limit of normal).
13. History or evidence of an autoimmune disorder considered clinically significant by the Investigator or requiring chronic use of systemic corticosteroids or other immunosuppressants.
14. Recent history (within 1 year of Screening) of alcohol or substance abuse as determined by the Investigator, a positive urine drug (due to non-prescription drug) or alcohol test at Screening, or use of cannabinoids (prescription or recreational).
15. Clinically significant systemic illness or serious infection (e.g., pneumonia, septicemia) within 30 days prior to or during Screening.
16. History of or positive test result for human immunodeficiency virus (HIV).
17. History of or positive test result at Screening for hepatitis C virus antibody or hepatitis B virus (defined as positive for hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb]). Subjects with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive hepatitis B surface antibody IgG, and positive HBcAb) are eligible to participate in the study (US Centers for Disease Control and Prevention's interpretation of the hepatitis B serology panel).
18. History of severe allergic or anaphylactic reactions, or history of hypersensitivity to any of the inactive ingredients in the drug product (refer to the IB for information on the clinical formulation).

19. Any other medical conditions (e.g., renal disease) that are not stable or controlled, or, which in the opinion of the Investigator, could affect the subject's safety or interfere with the study assessments.

Medications

20. Any medications that, in the opinion of the Investigator, may contribute to cognitive impairment, put the subject at higher risk for AEs, or impair the subject's ability to perform cognitive testing or complete study procedures.
21. Use of allowed chronic medications at doses that have not been stable for at least 4 weeks prior to Screening Visit 1 or use of AD medications (including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine) at doses that have not been stable for at least 8 weeks prior to Screening Visit 1.
22. Use of medications with platelet anti-aggregant or anti-coagulant properties (the use of aspirin at a prophylactic dose [≤ 325 mg daily] is allowed).
23. Use of illicit narcotic medication.
24. Vaccinations within 10 days prior to randomization (Day 1).
25. Participation in any active immunotherapy study targeting Aβ unless documentation of receipt of placebo is available.
26. Participation in any other passive immunotherapy study targeting Aβ within 48 weeks prior to Screening unless documentation of receipt of placebo is available.
27. Participation in any study with purported disease-modifying effect in AD within 26 weeks prior to Screening unless documentation of receipt of placebo is available. Subjects who developed ARIA-E during a previous disease-modifying trial should be excluded.
28. Participation in a previous study with aducanumab (subject is eligible if he/she did not receive active aducanumab).

Study Procedures

29. Contraindications to having a brain MRI (e.g., pacemaker; MRI-incompatible aneurysm clips, artificial heart valves, or other metal foreign body; claustrophobia that cannot be medically managed).
30. Contraindication to having a PET scan (e.g., inability to lie flat or still for the duration of the scan) or intolerance to previous PET scans (i.e., previous hypersensitivity reactions to any PET ligand or imaging agent, failure to participate in and comply with previous PET scans).
31. A negative PET scan result with any amyloid-targeting ligand within 24 weeks prior to Screening.
32. Have had or plan exposure to experimental radiation within 12 months prior to Screening such that radiodosimetry limits would be exceeded by participating in this study.

33. For subjects who consent to lumbar puncture (LP), any contraindications to having a LP (e.g., platelet count <100,000/µL, lumbar spine deformity). Any symptoms caused by or related to the optional LP during screening must be resolved prior to randomization. Subjects may still participate in the overall study even if participation in the optional LP portion is contraindicated.

Others

34. Female subjects who are pregnant or currently breastfeeding.
35. Previous participation in this study. Subjects who fail screening will be permitted to be rescreened once at the Sponsor's discretion, except those who fail due to PET, MMSE, CDR, hepatitis B or C, or abnormal MRI findings.
36. Subject currently living in an organized care facility with extensive intervention and/or support of daily living activities.
37. Blood donation (≥ 1 unit) within 1 month prior to Screening.
38. Inability to comply with study requirements.
39. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

8.3. Inclusion Criteria for Long-Term Extension

To be eligible to participate in the LTE, subjects must meet the following eligibility criteria at Week 78:

1. Subject must have completed the placebo-controlled period of the study including the Week 78 Visit. Subject must have taken at least 14 doses and not have missed more than 4 consecutive doses. Subjects who do not meet these criteria can enter the LTE only with Sponsor's approval.
2. MMSE score > 15 at the Week 78 Visit.
3. The subject (or the subject's legally authorized representative) has the ability to understand the purpose and risks of the study and provide signed and dated informed consent (or assent) and authorization to use confidential health information in accordance with national and local subject privacy regulations.
4. Female subjects of childbearing potential and male subjects must practice effective contraception during the study and for 24 weeks after their last dose of study treatment.
5. Apart from a clinical diagnosis of AD, the subject must be in good health as determined by the Investigator, based on medical history.
6. Must have the ability to comply with procedures for protocol-related tests.
7. Has one informant/care partner who, in the Investigator's judgment, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally be available by phone to provide information to the Investigator and study staff about the

subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study, and the use of the same informant/care partner for the duration of the study is encouraged.

8.4. Exclusion Criteria for Long Term Extension

Subjects will be excluded from entering the LTE if at Week 78 they have:

any medical or psychiatric contraindication or clinically significant abnormality that, in the opinion of the Investigator, will substantially increase the risk associated with the subject's participation in and completion of the study.

9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

9.1. Screening and Enrollment

Subjects (or their legally authorized representative, where applicable) must provide informed consent before any screening tests are performed (see Section 17.3). During Screening, subjects can complete the neurocognitive scales (CDR, MMSE and RBANS) to determine study eligibility under a separate initial consent process. If the subject meets inclusion criteria for these 3 scales the full consent process must be completed prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process which would allow the administration of all screening assessments. When a subject signs the full informed consent form (ICF), that subject is considered to be enrolled in the study.

The following tests should be repeated prior to dosing if they were performed > 60 days prior to Day 1: confirmation of eligibility criteria, abbreviated medical history, physical examination, ECG, hematology, blood chemistry, serum pregnancy test, and all neurocognitive assessments. Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log.

9.2. Randomization and Registration of Subjects

Subjects will be registered at the Screening Visit and randomized only after all baseline assessments have been completed and the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. No subject may begin treatment prior to assignment of a unique identification number (registration) and randomization. Any subject identification numbers or randomization schedule assignments that are assigned will not be reused even if the subject does not receive treatment. Rescreened subjects will be assigned a new number.

Subjects will be randomized to receive aducanumab low dose: aducanumab high dose: placebo in a 1:1:1 ratio. The randomization will be stratified by site and ApoE ε4 status (carrier or non-carrier), so that approximately 60% to 70% ApoE ε4 carriers are enrolled. Enrollment will also be monitored, via the IRT, such that the population of subjects with mild AD represents a small percentage of the total enrolled in the trial. Subjects who withdraw from the study may not be replaced.

Refer to the Study Reference Guide for details on registration and randomization.

9.3. Blinding Procedures

This study consists of a randomized, double-blind, placebo-controlled period, followed by a dose-blinded LTE with all subjects receiving aducanumab.

For the double-blinded placebo-controlled period, all study staff who conduct subject assessments will be blinded to the subject treatment assignments. The rating health care professionals should remain blinded to treatment assignment as well as subject care management and only have access to the information necessary to carry out their responsibilities as detailed in

Section 4.3.1. As a placebo match is not provided for the study, unblinded pharmacy staff are required to manage all aspects of study drug receipt, dispensing and preparation. To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Biogen or its representatives, except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded Quintiles or Biogen safety staff.

For the LTE, the dose information must remain restricted. The rating and treating health care professional should remain blinded to treatment assignment and only have access to the information necessary to carry out their responsibilities as detailed in Section 4.3.1. To maintain the study blind, it is imperative that dose information is not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Biogen or its representatives, except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded Quintiles or Biogen safety staff.

10. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

A subject *must* permanently discontinue study treatment for any of the following reasons:

- The subject develops any of the following:
  - ARIA-E accompanied by severe or serious clinical symptoms.
  - Symptomatic ARIA-H (microhemorrhages or superficial siderosis) with severe or serious clinical symptoms.
  - ARIA-H with ≥ 10 microhemorrhages and/or ≥ 2 focal areas of superficial siderosis.

  See Section 7.2.1 for full details regarding discontinuation and dose reduction due to ARIA-E or ARIA-H.
- The subject becomes pregnant. Study treatment must be discontinued immediately and pregnancy must be reported according to the instructions in Section 15.4.1.
- The subject withdraws consent to continue study treatment.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment or unblinding of the subject's treatment assignment.
- The subject experiences an AE that does not resolve or requires continued treatment that meets exclusionary criteria.
- The subject experiences a severe infusion reaction.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Investigator or Sponsor for noncompliance.

The reason for discontinuation of study treatment must be recorded in the subject's case report form (CRF).

Subjects who discontinue treatment should remain in the study and continue protocol-required tests and assessments until the end of the study or until the subjects withdraw consent.

10.2. Withdrawal of Subjects From Study

Subjects must be withdrawn from the study for any one of the following reasons:

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator or Sponsor.

The reason for the subject's withdrawal from the study must be recorded in the subject's CRF.

Subjects who are withdrawn from the study after receiving ≥1 doses of study treatment should complete the Early Termination (ET) Visit after the reason for withdrawal is identified. Subjects should return to the site as soon as possible to complete assessments as outlined in the Week 94 (Follow-up [FU]/ET) Visit if discontinuing during the double-blind period of the study or as outlined in the Week 198 (FU/ET) Visit if discontinuing from the LTE (see Section 4 for details).

11. STUDY TREATMENT USE

11.1. Regimen

Refer to and follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

Please see Section 4.2 (Schedule of Events) for the study drug infusion schedule during the placebo-controlled and LTE periods of the study.

Aducanumab is to be administered by IV infusion following dilution into saline. See Section 12 for details of aducanumab study treatment.

11.1.1. Aducanumab

The Sponsor will provide aducanumab to study sites.

11.1.2. Placebo

Placebo [redacted] sodium chloride) will be supplied by the study site.

11.2. Modification of Dose and/or Treatment Schedule

Refer to Section 7.2.1 (dose suspension) and Section 7.2.2 (infusion interruption). Doses should be administered at least 21 days apart. If the dosing interval cannot be met, the dose administration should be assessed by the study medical monitor.

11.3. Precautions

Not applicable.

11.4. Compliance

Compliance with treatment dosing is to be monitored and recorded by unblinded site staff.

11.5. Prior and Concomitant Therapy and Procedures

11.5.1. Prior and Concomitant Therapy

Prior AD medication use within the 12 months prior to screening will be captured.

A concomitant therapy is any drug or substance administered between the informed consent and the FU/ET Visit (Week 94 or Week 198).

No premedication (e.g., anti-allergy drugs, antipyretic analgesics) should be used prior to the start of study drug infusion unless discussed with the study medical monitor in advance.

11.5.1.1. Allowed Concomitant Therapy

- Medications for chronic conditions are allowed at a stable dose during the study as long as the subject has been stable on the medication(s) for at least 4 weeks prior to Screening Visit 1.
- Symptomatic therapies for AD, including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine, are allowed provided that subjects are receiving a stable dose for at least 8 weeks prior to Screening Visit 1 and that they stay on a stable dose while in the study.
- Vaccinations with live or attenuated vaccines are allowed during the study. Administration of any vaccination/booster should not be given < 10 days prior to any dosing visit and for 10 days after a dosing visit.

11.5.1.2. Disallowed Concomitant Therapy

- Medications with platelet anti-aggregant or anti-coagulant properties, except the use of aspirin at a dose of ≤ 325 mg per day.
- Non-prescription narcotic medication.
- Immunosuppressive drugs (including systemic corticosteroids). Local corticosteroids and certain systemic corticosteroids may be permitted at the Sponsor's discretion.
- Parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange, and plasmapheresis.
- Any investigational drug.

Subjects should be instructed to continue the medications that they were receiving at enrollment (see allowed concomitant therapy above) and avoid starting any new medications or herbal preparations during the study period, as it may confound the results of the study. However, medically indicated medication or treatment should not be withheld. Subjects should inform the Investigator of any changes in medication. The change should be reviewed by the Investigator and the study medical monitor to determine whether the subject's study treatment should be suspended, with the exception of medications used to treat AEs, which would not result in automatic withdrawal. Biogen may be consulted if required.

Subjects should have an unscheduled visit for a change in AD medication, and all clinical assessments for the primary and secondary objectives should be performed prior to the change in medication.

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, routine colonoscopy, bacterial cultures) performed between the time the subject is enrolled in the study and the FU/ET Visit, unless the subjects is being followed for study-related toxicity.

The use of concomitant therapies or procedures defined above must be recorded on the subject's CRF. AEs related to administration of these therapies or procedures must be documented on the appropriate AE CRF.

11.6. Continuation of Treatment

No further provisions are made for access to the study treatment. If aducanumab is proven to be beneficial, all regulatory requirements regarding poststudy access will be met.

12. STUDY TREATMENT MANAGEMENT

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Study treatment vials are for one-time use only; any study treatment remaining in the vial must not be used for another subject.

12.1. Aducanumab

Research Name: BIIB037

Generic Name: Aducanumab

Trade Name(s): Not applicable

Synonyms: Fully human, IgG_1, anti-Aβ monoclonal antibody

Aducanumab is a recombinant human antibody expressed in a Chinese hamster ovary cell line (41-3D17), purified to a high degree of purity and formulated as a liquid. Aducanumab is an IgG_1 consisting of 2 heavy and 2 kappa light chains connected by inter-chain disulfide bonds. Aducanumab has 1 carbohydrate moiety linked to Asn-304. Aducanumab is purified from the media and formulated as a liquid.

Aducanumab is supplied as a liquid drug product containing aducanumab CCI sodium citrate CCI citric acid CCI L-arginine hydrochloride CCI polysorbate 80 CCI (weight/volume), pH 6.3. Aducanumab is manufactured in accordance with Good Manufacturing Practices.

The contents of the label will be in accordance with all applicable regulatory requirements. Aducanumab should not be used after the expiration date.

12.1.1. Aducanumab Preparation

The individual preparing aducanumab should carefully review the instructions provided in the DHA.

Aducanumab is to be administered by IV infusion following dilution into saline.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the vials or drug it should not be used. The vial in question should be saved at the study site, and the problem immediately reported to Biogen.

12.1.2. Aducanumab Storage

Study treatment must be stored in a secure location. Aducanumab is to be stored at 2° to 8°C (36°F to 46°F), in a locked storage container with limited access. Aducanumab should be protected from light, protected from freezing, and should not be shaken. If administration of the prepared aducanumab is delayed for more than 2 hours, then it should be kept at 2° to 8ºC until use. If administration of the prepared aducanumab is delayed for more than 24 hours, it must be discarded. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

12.1.3. Aducanumab Handling and Disposal

The Investigator must return all used and unused vials of aducanumab as instructed by Biogen (or its designee), unless approved for onsite destruction.

If any aducanumab supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from Biogen by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Biogen must be notified in writing of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. Aducanumab Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), and accounts of any study treatment accidentally or deliberately destroyed.

Unless otherwise notified, all vials both used and unused, must be saved for study treatment accountability. By the end of the study reconciliation must be made between the amount of aducanumab supplied, dispensed, and subsequently destroyed or returned to Biogen. A written explanation must be provided for any discrepancies.

12.2. Placebo

The placebo CCI sterile sodium chloride for injection) will be provided by the site in the form of 100 ml saline IV bags.

12.3. Additional Protocol-Designated Products

Refer to the DHA for infusion-related supply specifications.

For details on PET imaging ligands, refer to the procedural manual for PET.

13. EFFICACY, PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS

Refer to Section 4.2 for the timing of assessments.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of aducanumab:

- CDR
- MMSE
- ADAS-Cog 13
- ADCS-ADL-MCI
- NPI-10

It is recommended that clinical assessments be performed at the same time of day for patients during their study visits.

Some tests will require the informant/care partner to participate and answer questions regarding the subject's daily activities and cognitive capabilities.

The order of administration of the clinical assessments is described in the Study Reference Guide.

13.2. Pharmacokinetic Assessments

Serum concentrations of aducanumab will be measured using a validated assay.

13.3. Pharmacodynamic Assessments

The following tests will be performed to assess the pharmacodynamic properties of aducanumab:

- Serial measurement of amyloid plaque burden in certain areas of the brain as measured by amyloid PET (in a subset of approximately 400 subjects participating in the PET cohort).

  Only sites with capabilities of performing ^{18}F-florbetapir PET will be allowed to perform this assessment. Investigator participation in this part of the study is optional and contingent upon approval by his/her ethics committee (EC) or institutional review board (IRB). If the Investigator is not participating or the test is not approved by his/her EC/IRB, the relevant section of the ICF will not be applicable to that site.

  Subject participation in this part of the study is optional at participating sites. Informed consent must be recorded in the CRF. Detailed PET scanning protocols will be described in a separate procedural manual for PET. Approximately 400 subjects are expected to participate in this part of the study.

- Whole brain volume, hippocampal volume, ventricle volume, and cortical gray matter volume measured by MRI.

  Detailed MRI scanning protocols will be described in the procedural manual for MRI.

- Functional connectivity as measured by tf-fMRI (in a subset of sites and subjects).

  Only sites with capabilities of performing tf-fMRI will be allowed to perform this assessment. Detailed tf-fMRI scanning protocols will be described in the procedural manual for MRI.

- Cerebral blood flow as measured by ASL-MRI (in a subset of sites and subjects).

  Only sites with capabilities of performing ASL-MRI will be allowed to perform this assessment. Detailed ASL-MRI scanning protocols will be described in the procedural manual for MRI.

- Disease-related blood and CSF biomarkers. Subject participation in CSF collection is optional (see Section 13.4.1).

13.4. Additional Assessments

13.4.1. CSF Biomarkers (Lumbar Puncture Test)

An optional CSF collection will be conducted at sites. Investigator participation in this part of the study is optional and contingent upon approval by the site's EC/IRB. If the Investigator is not participating or the test is not approved by the site's EC/IRB, the relevant section of the ICF will not be applicable to that site.

Subject participation in the LP test is optional at participating sites. Informed consent must be recorded in the CRF.

Analyses of CSF samples will include, but are not limited to, the following:

- Disease-related biomarker levels (amyloid and tau proteins).
- Cell count and differential (to be conducted by the local laboratory).
- Total protein, (to be conducted by the central laboratory).

Four LPs are to be performed (1 at Screening, 1 in the placebo-controlled period, and 2 in the LTE). Any symptoms caused by or related to the LP must be resolved or stabilized, in the opinion of the Investigator, prior to infusion. Vital signs will be obtained before the LP at each visit for subjects participating. Guidance on LPs will be provided in the Study Reference Guide.

13.4.2. ApoE genotyping

Whole blood samples for deoxyribonucleic acid (DNA) ApoE genotyping will be collected from all subjects at the Screening Visit.

13.4.3. Optional DNA Test

Additional whole blood samples for DNA analysis will be collected only for subjects that consent to this optional test. Samples will be collected and archived according to the guideline in the laboratory manual to support discovery and verification of biomarkers related to AD or aducanumab pharmacology.

13.4.4. Health Outcomes Assessments

The following assessments will be performed to evaluate the effect of aducanumab in subjects and caregivers:

- EQ-5D (SR)
- EQ-5D (IR-S)
- EQ-5D (IR-I)
- mPDQ-20
- Caregiver burden questionnaire

Some tests will require the informant/care partner to participate and answer questions regarding the subject's daily activities and cognitive capabilities.

The order of administration of the clinical assessments is described in the Study Reference Guide.

14. SAFETY ASSESSMENTS

See Section 4.2 for the timing of assessments.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of aducanumab:

- AE and SAE monitoring.
- Physical examination, including height and weight.
- Neurological examination.
- Vital signs (body temperature, heart rate, SBP, DBP, and respiratory rate).
- 12-lead ECG.
- Brain MRI.
- Concomitant medication, therapy and procedure monitoring.
- MOCA (for ARIA monitoring and management).
- Columbia Suicide Severity Rating Scale.

14.2. Laboratory Safety Assessments

The following laboratory assessments will be performed to evaluate the safety profile of aducanumab

- Hematology: complete blood count with differential and platelet count, and absolute neutrophil count.
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, ALT, AST, lactate dehydrogenase, gamma-glutamyl-transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, potassium.
- Urinalysis: color, specific gravity, pH, protein, glucose, blood ketones, and microscopic examination (if abnormal).
- Serum and urine pregnancy test for women of childbearing potential only.
- Coagulation, virology (including HIV if dictated by local law), HbA_{1c}, and alcohol/drug screen at Screening.

14.3. Immunogenicity Assessments

Presence of serum anti-aducanumab will be determined using a validated assay. A standard 3-tier anti-drug antibody (ADA) approach will be used (i.e., screening assay, confirmatory assay,

and titration assay). Confirmed antidrug antibody-positive samples will be tested for the presence of anti-aducanumab neutralizing antibodies using a validated assay.

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject or his/her legally authorized representative must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Determination of whether an abnormal laboratory value meets the definition of an AE will be made by the Investigator. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE.
- A laboratory test result that requires the subject to receive specific corrective therapy.
- A laboratory abnormality that the investigator considers to be clinically significant.

15.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes

listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

15.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject is hospitalized. The study site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
    - If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 15.1.2 is met.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2.
- The relationship of the event to study treatment as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment.

Relationship of Event to Study Treatment	
Not related	An AE will be considered "not related" to the use of the investigational drug if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include but are not limited to: the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of the investigational drug if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of an alternative explanation for the AE.

15.2.3. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by Biogen according to the IB for aducanumab.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and the FU/ET visit is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment.

15.3.2. Adverse Events of Special Interest

ARIA-E and ARIA-H are considered AEs of special interest and will be entered on the Adverse Event of Special Interest CRF within 72 hours following the receipt of abnormal MRI findings from the central MRI reader.

AE reporting for ARIA-E and ARIA-H will be based on the following centrally read MRI sequences: fluid attenuated inversion recovery/T2 for ARIA-E and T2*/gradient echo for ARIA-H.

If the event qualifies as an SAE an SAE form should be submitted per the guidelines in Section 15.3.4. Investigators should include a copy of the centrally read MRI report when submitting the SAE form to Quintiles Lifecycle Safety.

15.3.3. Serious Adverse Events

Any SAE experienced by the subject between the time of the signing of the ICF and the FU/ET visit is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to Biogen (or designee) within 24 hours as described in Section 15.3.4. Follow-up information regarding an SAE also must be reported with 24 hours.

Events occurring after the FU/ET visit should be reported to Biogen only if the investigator considers the SAE related to study treatment.

Any SAE that is ongoing when the subject completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

15.3.4. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify Quintiles Lifecycle Safety within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any SAE that occurs between the time that the subject has signed the ICF and the FU/ET Visit must be reported to Quintiles Lifecycle Safety) within 24 hours of the study site staff becoming aware of the event. Thereafter, the event should be reported only if the Investigator considers it related to study treatment.

A report ***must be submitted*** to Quintiles Lifecycle Safety regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject has received study treatment
- The severity of the event
- The relationship of the event to study treatment

To report initial or follow-up information on an SAE, fax or email a completed SAE form. Refer to the Study Reference Guide for country-specific Quintiles Lifecycle Safety fax numbers or email PPD

15.3.4.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Quintiles Lifecycle Safety. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.5. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen to be related to the study treatment administered.

Appropriate personnel in Biogen Safety and Benefit Risk (SABR) will unblind SUSARs for the purpose of regulatory reporting. Biogen or designee will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Biogen or designee will submit SUSARs to Investigators in a blinded fashion.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

Subjects should not become pregnant or impregnate their partners during the study and for 24 weeks after their last dose of study drug. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy occurring in a female subject by faxing the appropriate form to Quintiles Lifecycle Safety within 24 hours of the study site staff becoming aware of the pregnancy at the SAE reporting fax number provided in the study reference manual. The Investigator or study site staff must report the outcome of the pregnancy to Quintiles Lifecycle Safety.

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period.

15.4.2. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on an Overdose form and faxed to Quintiles Lifecycle Safety within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Quintiles Lifecycle Safety even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed to Quintiles Lifecycle Safety). All study treatment-related dosing information must be recorded on the dosing CRF.

15.4.3. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator (or designee) should contact the Quintiles 24-hour emergency medical support number. Refer to the Study Reference Guide's Official Contact List for complete contact information.

15.4.3.1. Unblinding for Medical Emergency

In this study, emergency decoding will be made available to the Investigator and designated personnel at Biogen through IRT.

In a medical emergency when knowledge of the subject's treatment assignment may possibly influence the subject's clinical care, the Investigator may access the subject's treatment assignment by IRT. However, prior to unblinding, the Investigator can contact the Quintiles 24-hour emergency medical support number at PPD

The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, nor to personnel involved with the analysis and conduct of the study.

15.5. Contraception Requirements

For the purposes of this study, women of childbearing potential are defined as all women physiologically capable of becoming pregnant, UNLESS they meet one of the following conditions:

- Postmenopausal: 12 months of natural (spontaneous) amenorrhea without an alternative medical cause or 6 weeks after surgical bilateral oophorectomy with or without hysterectomy.
- Post hysterectomy.
- Female surgical sterilization (e.g., bilateral tubal ligation).

For the purposes of the study, highly effective contraception is defined as use of 1 of the following:

- For females of childbearing potential:
  - Established use of oral, injected, or implanted hormonal methods of contraception.
  - Placement of an intrauterine device or intrauterine system.
  - Barrier methods of contraception with use of a spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide.

  - Male sexual partners underwent surgical sterilization with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate.

- For males:
  - Vasectomy with negative semen analysis at follow-up.
  - Use of condoms with spermicide.
- For males and females of childbearing potential:
  True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies and follow up on the outcome of the pregnancy in female subjects.
- Complete an SAE form for each SAE and fax it to Biogen SABR (or designee) within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to Biogen SABR (or designee) within 24 hours of the study site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE follow-up information, if possible, until the event has resolved or become stable.
- Report SAEs to local EC/IRBs, as required by local law.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor (Quintiles) is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen (or designee) is to notify all appropriate regulatory authorities, central EC/IRBs, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Demography and Baseline Disease Characteristics

Demographics and baseline data will be summarized by treatment group with summary statistics (mean, standard deviation [SD], median, and range) or with frequency distributions.

16.2. Efficacy and Pharmacodynamics

16.2.1. Analysis Population

The intent-to-treat (ITT) population, defined as all subjects who were randomized and received at least 1 dose of study treatment (aducanumab or placebo), will be used for the efficacy analyses. For each endpoint, additional conditions may apply to the definition of the population for the analysis. Subjects will be analyzed in the groups to which they were randomized.

16.2.2. Methods of Analysis

16.2.2.1. General Considerations

Summary statistics will be presented. For continuous endpoints, summary statistics will generally include: number of subjects with data, mean, standard deviation, median, and range. For categorical endpoints, this will generally include: number of subjects randomized or dosed, number with data, and the percent of those with data in each category. Statistical testing for efficacy endpoints will be made between each aducanumab regimen and placebo. All statistical tests will be 2-sided.

16.2.2.2. Dose Regimens to be Evaluated

The following dose regimens of aducanumab as compared with placebo will be evaluated

- Aducanumab high-dose regimen (6 mg/kg in ApoE ε4 carriers and 10 mg/kg in ApoE ε4 non carriers).
- Aducanumab 6 mg/kg dose regimen (6 mg/kg in ApoE ε4 carriers and ApoE ε4 non-carriers).
- Aducanumab low-dose regimen (3 mg/kg in ApoE ε4 carriers and 6 mg/kg in ApoE ε4 non-carriers).

In the event that the proposed maximum dose (10mg/kg in ApoE ε4 non-carriers or 6 mg/kg in ApoE ε4 carriers) is terminated after the start of the study (Section 5.3.2) the definition of aducanumab high dose regimen and aducanumab low dose regimen will be modified as shown in Table 10. The dosing modification will be entirely based on interim analysis of outcomes that are independent of, and uninformative about, the treatment-related efficacy effect. Control of

Type I error rate is thus maintained without a statistical adjustment for such adaptations[Chow and Chang 2011].

Table 10: Dose Group Pooling Strategy in the Event of Treatment Group Termination

Treatment group(s) Terminated	Definitions of Revised Pooled Treatment Groups for Comparison
ApoE ε4 carrier high-dose group(6 mg/kg)	Low: ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg High: ApoE ε4 carrier 3 mg/kg and non-carrier 10 mg/kg
ApoE ε4 non-carrier high-dose group (10 mg/kg)	Low: ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg High: ApoE ε4 carrier 6 mg/kg and non-carrier 6 mg/kg
ApoE ε4 carrier high-dose group(6 mg/kg) AND ApoE ε4 non-carrier high-dose group(10 mg/kg)	ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg

16.2.2.3. Considerations for Multiple Comparison Adjustments

A sequential (closed) testing procedure will be used to control the overall Type I error rate due to multiple comparisons for the primary endpoint. The order of treatment comparisons is as follows: aducanumab high-dose regimen versus placebo, aducanumab 6 mg/kg regimen versus placebo, and aducanumab low-dose regimen versus placebo. In the event of a dosing modification (see Table 10), the first comparison is the aducanumab high-dose regimen versus placebo and the second comparison is the aducanumab low-dose regimen versus placebo. If the first comparison is statistically significant ($p \leq 0.05$), then the second comparison will also be made at the 0.05 α level. If the second comparison is statistically significant ($p \leq 0.05$), then the third comparison will also be made at the 0.05 α level. However, all comparisons after the initial comparison with $p > 0.05$ will not be considered statistically significant.

Secondary endpoints have been rank prioritized, in the order shown in Section 6. In order to control for a Type I error for the secondary endpoints, a sequential closed testing procedure will be used and will include both the order of the secondary endpoints and treatment comparisons. Specifically, for each of the secondary endpoints, a sequential (closed) testing procedure, as for the primary endpoint, will be used to control the overall Type I error rate due to multiple treatment comparisons. If statistical significance is not achieved for one, two or all three comparisons, all endpoint(s) of a lower rank will not be considered statistically significant for 1, 2 or all 3 comparisons, respectively.
Due to a current lack of scientific consensus in the AD field on which biomarker(s) might be most appropriate, the selection of the biomarkers and methodology for control of Type I error will be pre-specified in the statistical analysis plan (SAP). Otherwise, there will be no multiple comparison adjustments for the tertiary endpoints.

16.2.2.4. Analysis of the Primary Endpoint

The population for the primary endpoint analysis will be subjects in the ITT population with a baseline and at least one post-baseline CDR-SB score. A mixed model repeated measures (MMRM) model will be used as the primary analysis to analyze change from baseline CDR-SB using fixed effects of treatment, time, treatment-by-time interaction, baseline CDR-SB, baseline CDR-SB by time, baseline MMSE, and baseline ApoE ε4 status.

16.2.2.5. Analysis of the Secondary Endpoints

16.2.2.5.1. Change from Baseline to Week 78 in MMSE

The population for the analysis will be subjects in the ITT population with a baseline and at least one post-baseline MMSE value. A MMRM model will be used as the primary analysis to analyze change from baseline MMSE using fixed effects of treatment, time, treatment-by-time interaction, baseline MMSE value, baseline MMSE by time interaction and baseline ApoE ε4 status

16.2.2.5.2. Change from Baseline to Week 78 in ADAS-Cog 13

The population will be subjects in the ITT population with a baseline and at least one post-baseline ADAS-Cog 13 score. A MMRM model will be used as the primary analysis to analyze change from baseline ADAS-Cog 13 using fixed effects of treatment, time, treatment-by-time interaction, baseline ADAS-Cog 13, baseline ADAS-Cog 13 by time interaction; baseline MMSE and baseline ApoE ε4 status.

16.2.2.5.3. Change from Baseline to Week 78 in ADCS-ADL-MCI

The population will be subjects in the ITT population with a baseline and at least one post-baseline ADCS-ADL-MCI score. A MMRM model will be used as the primary analysis to analyze change from baseline ADCS-ADL-MCI using fixed effects of treatment, time, treatment-by-time interaction, baseline ADCS-ADL-MCI, baseline ADCS-ADL-MCI by time interaction; baseline MMSE and baseline ApoE ε4 status.

16.2.2.6. Tertiary Endpoints Analysis

16.2.2.6.1. Placebo-Controlled Period

Where appropriate, a MMRM model will be used as the primary analysis to analyze change from baseline using fixed effects of treatment, time, treatment by time interaction, baseline value, baseline value by time interaction, baseline MMSE and baseline ApoE ε4 status.

Otherwise, an analysis of covariance or its non-parametric equivalent may be used to analyze these exploratory endpoints.

16.2.2.6.2. Long-Term Extension

The additional endpoints for the LTE are change from baseline over the placebo-controlled and LTE periods of the study. Analyses will be presented by treatment group in the

placebo-controlled period using the placebo-controlled period baseline. Details of the analyses will be pre-specified in the SAP.

16.3. Pharmacokinetics

16.3.1. Analysis Population

The population for PK analysis is defined as all subjects who were randomized, were dosed with study treatment, and had at least 1 measurable aducanumab concentration in serum.

16.3.2. Method of Analysis

The population PK characteristics of aducanumab will be determined by nonlinear mixed effects approach. Covariates that might influence the disposition of aducanumab (e.g., body weight, age, sex, immunogenicity, ApoE ε4 status) will be evaluated and the potential exposure-response relationships will be explored.

16.4. Safety

16.4.1. Analysis Population

The safety population is defined as all subjects who received at least 1 dose of study treatment (including placebo and aducanumab).

16.4.2. Methods of Analysis

All AEs, laboratory data, ECG, neurological and physical examinations and vital signs will be evaluated for safety.

16.4.2.1. Adverse Events

Only treatment-emergent adverse events (TEAEs) will be presented in the summary tables. Treatment emergent is defined as having an onset date that is on or after the start of study treatment, or as worsening after the start of study treatment.

Incidence of TEAEs will be summarized by treatment groups, overall, by severity, and by relationship to study treatment for the placebo-controlled period and over the 24-month LTE. The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

16.4.2.2. Clinical Laboratory Results

Laboratory data will be summarized using shift tables. Shifts from baseline to high/low status for hematology and blood chemistry parameters, and shifts from baseline to high/positive status for urinalysis will be presented. In addition, the shift from baseline to the maximum post-baseline value and the shift from baseline to the minimum post-baseline status will be presented for each laboratory test by treatment group. Also, summaries of laboratory values categorized

based on common toxicity criteria grade will be created. Summary statistics for actual values and change from baseline will also be presented for quantitative laboratory data.

16.4.2.3. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities.

16.4.2.4. ECG

The number and percentage of subjects with shifts to categorical values (abnormal not AE, or abnormal AE) will be summarized by treatment group.

16.4.2.5. Columbia Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale data will be summarized by treatment group.

16.5. Immunogenicity Data

16.5.1. Analysis Population

The analysis population for immunogenicity is defined as all subjects in the safety population who have at least 1 post-dose sample evaluated for immunogenicity.

16.5.2. Methods of Analysis

Anti-aducanumab serum antibodies will be summarized using shift tables.

16.6. Interim Analyses

16.6.1. Interim Futility Analysis

An interim analysis for futility of the primary endpoint will occur after approximately 50% of the subjects have completed the Week 78 Visit (or discontinued). In order to maintain the treatment blind, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim futility analysis. This independent group will present the unblinded interim analysis to the IDMC. The IDMC may recommend terminating the study for futility if it is evident that the efficacy of aducanumab is unlikely to be achieved.

The futility criteria will be discussed in detail in the SAP.

16.6.2. Interim Superiority Analysis

An interim analysis for superiority will be performed after approximately 50% of the subjects have completed the Week 78 Visit (or discontinued). The Lan-Demets method with O'Brien-Fleming stopping boundary for efficacy will be used. In order to maintain the treatment blind, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim superiority analysis. The independent group will present the unblinded interim analysis to the IDMC. The aim of this interim analysis is to allow the possibility to demonstrate treatment effect early. The analysis will be discussed in detail in the SAP.

16.7. Sample Size Considerations

The study's sample size is based, in part, on results from a protocol-specified interim analysis from Study 221AD103 which included 1 year data from 1, 3 and 10 mg/kg treatment groups.

A sample size of 450 subjects per treatment group will have approximately 90% power to detect a true mean difference of 0.5 in change from baseline CDR-SB at Week 78 between the 2 treatment groups. This power calculation is based on a 2-sided t-test assuming equal variance with a final significance level of 0.05, a SD of 1.92 and a drop-out rate of 30%. The SD estimate of 1.92 for Week 78 reflects a 39% increase over the SD from the protocol-specified interim analysis of 1-year data.

The assumed true mean difference of 0.5 between the 2 treatment groups represents an approximately 25% reduction in the placebo mean change from baseline at Week 78 if the placebo mean change is estimated to be 2.

The sample size may be reassessed in a blinded manner approximately 3 months before enrollment is complete if at least 15% of the data are available on the primary endpoint. At this interim time-point, the SD for the primary endpoint will be estimated based on the blinded data. The sample size may be increased if the SD is estimated to be more than approximately 2.07. In addition, the sample size could be increased using external clinical trial results that become available after the start of the study.

17. ETHICAL REQUIREMENTS

Biogen, Quintiles, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated

17.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

17.2. Ethics Committee/Institutional Review Board

The Investigator must obtain EC/IRB approval of the protocol, ICF, and other required study documents prior to starting the study. Biogen will submit documents on behalf of the investigational sites worldwide in compliance with local requirements.

If the Investigator makes any changes to the ICF, Biogen must approve the changes before the ICF is submitted to the EC. A copy of the approved ICF must be provided to Biogen. After approval, the ICF must not be altered without the agreement of the relevant EC and Biogen.

It is the responsibility of the Investigator(s) to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

Biogen must receive a letter documenting EC/IRB approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the EC/IRB at required intervals and not less than annually.

At the completion or termination of the study, the investigational site must submit a close-out letter to the EC/IRB and Biogen

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject’s legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations. Subjects can complete the neurocognitive scales (CDR, MMSE and RBANS) as an initial screening under a separate consent process. If the subject meets inclusion criteria for these 3 scales, the full consent process must be completed

prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process that would allow the administration of all screening assessments.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject (or the subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

A copy of the signed and dated ICF must be given to the subject, caregiver and/or legally authorized representative. The signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the subject's medical record.

17.4. Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., Protected Health Information authorization in North America).

The subject will not be identified by name in the CRF or in any study reports and these reports will be used for research purposes only. Biogen, its partner(s) and designee(s), EC/IRBs, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

17.5. Compensation for Injury

Biogen maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in Biogen or its partner[s]) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

Biogen will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by Biogen. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

During and/or after completion of the study, quality assurance officers named by Biogen or the regulatory authorities may wish to perform onsite audits. The Investigator will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested.

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor(s) will visit the Investigator(s) at regular intervals during the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contract(s) between the institution, Investigator, and Biogen.

18.5. Publications

Details are included in the clinical trial agreement for this study.

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

19.1.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of SAE reports. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or randomized, the IRT vendor will provide each study site with appropriate training, access rights and a user manual

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a web-based electronic data capture (EDC) tool developed by Quintiles and configured by the EDC vendor.

19.1.4. Central Laboratories for Laboratory Assessments

Biogen has selected a central laboratory service to perform all standard hematology, blood chemistry, and urinalysis testing for the study. This central laboratory will also receive, track, and ship all urine, blood, CSF samples, and DNA for specialized ApoE ε4 genotyping, PK, biomarker, and ADA testing, including aliquots from these samples retained as backup in case original samples are lost or not evaluable. Blood samples collected for future DNA testing will be processed to purify DNA and stored by the central laboratory.

Laboratories performing specialized testing will be identified in regulatory documentation. These laboratories will use appropriately validated or qualified assays to test study samples.

19.1.5. Central Facility for Other Assessments

A central imaging laboratory has been selected by Biogen to read and interpret all MRIs for this study within the timeframe specified in the procedural manual for MRI. In cases of ARIA-E and ARIA-H, the central imaging laboratory must expedite notification to the Principal Investigator and the Sponsor. For the purposes of study conduct, the MRI interpretations from the central reader will prevail over those from the local radiologist.

The central imaging laboratory will also collect PET scans and assess the screening scan for eligibility criteria.

19.1.6. Neurocognitive Assessments

Biogen selected a rater management group to establish rater qualification, study specific training and oversight. The study raters are required to complete qualifications steps and required training prior to administering study assessments. The rater management group will oversee the assessments per project-specific plans.

19.2. Study Committees

19.2.1. Advisory Committee

An advisory committee will be formed to provide scientific and medical direction for the study and to oversee the administrative progress of the study. The advisory committee will meet at least 4 times a year to monitor subject accrual and to monitor compliance with the protocol at individual study sites. The advisory committee will be blinded to subject treatment assignments during the study.

Members of the advisory committee will include external experts in AD medicine and statistics. Biogen will designate one of the participating Investigators to be the chairperson of the advisory committee.

19.2.2. Independent Data Monitoring Committee

The IDMC will be formed to review ongoing safety and tolerability data. Members of the IDMC will not be allowed to participate as investigators in this study. The IDMC will review safety data on an ongoing basis to ensure safe and proper treatment of subjects. The IDMC, based on the nature, frequency, and/or severity of an AE(s) may recommend protocol modification(s), dose suspension, dose termination or study termination. An IDMC charter will provide full guidance on the function and practices to be followed by the IDMC.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the EC/IRB and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the EC/IRB before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, Biogen may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Sections 17.2 and 17.3).

19.4. Ethics Committee/Institutional Review Board Notification of Study Completion or Termination

Where required, the regulatory authorities and EC/IRBs must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator must notify Biogen of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

Biogen will designate one or more of the participating Study Investigators as a signatory for the study report. This determination will be made by several factors including but not limited to the Investigator's experience and reputation in the studied indication, the Investigator's contribution to the study in terms of design, management, and/or subject enrollment, or by other factors determined to be relevant by Biogen.

20. REFERENCES

Albert MS, DeKosky ST, Dickson D, 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(3):270-9.

Alzheimer's Disease International. World Alzheimer Report 2014: Dementia and risk reduction. London: Alzheimer's Disease International (ADI); 2014.

Chow S, Chang M. Adaptive Design Methods in Clinical Trials, Second Edition. Second Edition ed. Boca Raton, FL: Chapman and Hall/CRC; 2011.

Doody RS, Thomas RG, Farlow M, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med. 2014;370(4):311-21; correspondence N Engl J Med. 2014;370(15):1459-60.

Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol. 2010;9(11):1118-27.

Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 2014;13(6):614-29.

Fagan T. Crenezumab Disappoints in Phase 2, Researchers Remain Hopeful. Conference Coverage Series: Alzheimer's Association International Conference (AAIC) 2014 [Internet]. Alzforum Web site. 2014 Jul 22 [cited 2014 Oct 04]. Available from: http://www.alzforum.org/news/conference-coverage/crenezumab-disappoints-phase-2-researchers-remain-hopeful.

Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002;297(5580):353-6. Epub 2002 Jul 20.

Hock C, Konietzko U, Streffer JR, et al. Antibodies against beta-amyloid slow cognitive decline in Alzheimer's disease. Neuron. 2003;38(4):547-54. Epub 2003/05/27.

Jack CR, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013;12(2):207-216.

Koffie RM, Meyer-Luehmann M, Hashimoto T, et al. Oligomeric amyloid beta associates with postsynaptic densities and correlates with excitatory synapse loss near senile plaques. Proc Natl Acad Sci U S A. 2009;106(10):4012-7.

Kuchibhotla KV, Goldman ST, Lattarulo CR, et al. Abeta plaques lead to aberrant regulation of calcium homeostasis in vivo resulting in structural and functional disruption of neuronal networks. Neuron. 2008;59(2):214-25.

Kumar-Singh S, Pirici D, McGowan E, et al. Dense-core plaques in Tg2576 and PSAPP mouse models of Alzheimer's disease are centered on vessel walls. American Journal of Pathology. 2005;167(2):527-43. Epub 2005/07/29.

Lenderking WR, Steenrod A, Rüdell K, et al. Options for Evaluating Treatment Benefit in MCI and Prodromal Alzheimer's Disease: Content Validity of the Perceived Deficits Questionnaire (PDQ) in Patients with Early Symptoms of Cognitive Decline. Advances in Alzheimer's Disease. 2014;3:1-10. Epub March 2014.

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. Alzheimer's and Dementia. 2011;7(3):263-269.

Meyer-Luehmann M, Spires-Jones TL, Prada C, et al. Rapid appearance and local toxicity of amyloid-beta plaques in a mouse model of Alzheimer's disease. Nature. 2008;451(7179):720-4.

Morris JC, Blennow K, Froelich L, et al. Harmonized diagnostic criteria for Alzheimer's disease: recommendations. J Intern Med. 2014;275(3):204-13.

Ostrowitzki S, Deptula D, Thurfjell L, et al. Mechanism of amyloid removal in patients with Alzheimer disease treated with gantenerumab. Arch Neurol. 2012;69(2):198-207. Epub 2011 Oct 10.

Pfeifer M, Boncristiano S, Bondolfi L, et al. Cerebral hemorrhage after passive anti-Abeta immunotherapy. Science. 2002;298(5597):1379. Epub 2002/11/16.

Racke MM, Boone LI, Hepburn DL, et al. Exacerbation of cerebral amyloid angiopathy-associated microhemorrhage in amyloid precursor protein transgenic mice by immunotherapy is dependent on antibody recognition of deposited forms of amyloid beta. J Neurosci. 2005;25(3):629-36. Epub 2005/01/22.

Rozkalne A, Spires-Jones TL, Stern EA, et al. A single dose of passive immunotherapy has extended benefits on synapses and neurites in an Alzheimer's disease mouse model. Brain Res. 2009;1280:178-85.

Sperling RA, Jack Jr CR, Black SE, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: Recommendations from the Alzheimer's Association Research Roundtable Workgroup. Alzheimers Dement. 2011;7(4):367-385.

Spires-Jones TL, Mielke ML, Rozkalne A, et al. Passive immunotherapy rapidly increases structural plasticity in a mouse model of Alzheimer disease. Neurobiol Dis. 2009;33(2):213-20.

Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke. 2001;32(6):1318-22.

Weller RO, Subash M, Preston SD, et al. Perivascular drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and Alzheimer's disease. Brain Pathol. 2008;18(2):253-66.

Wilcock DM, Colton CA. Immunotherapy, vascular pathology, and microhemorrhages in transgenic mice. CNS Neurol Disord Drug Targets. 2009;8(1):50-64. Epub 2009/03/12.

Winkler DT, Bondolfi L, Herzig MC, et al. Spontaneous hemorrhagic stroke in a mouse model of cerebral amyloid angiopathy. J Neurosci. 2001;21(5):1619-27. Epub 2001/02/27.

21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease", and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

Biogen MA Inc.
225 Binney Street
Cambridge, MA 02142
United States

PROTOCOL NUMBER: 221AD301

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead Berkshire
SL6 4AY
United Kingdom

PHASE OF DEVELOPMENT: 3

PROTOCOL TITLE: A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease

EUDRA CT NO: **2015-000966-72**

DATE: 28 June 2018
Version 6.0
FINAL

Supersedes previous Version 5.0 dated 18 September 2017.

SPONSOR SIGNATURE

Protocol 221AD301 was approved by:

PPD

2 July 2018

Date

Biogen MA Inc.

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1. SPONSOR INFORMATION

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103-0027
Japan

For 24-hour emergency medical support contact

IQVIA at PPD

Please refer to the Study Reference Manual for complete contact information.

Biogen may transfer any or all of its study-related responsibilities to a contract research organization (CRO) and other third parties; however, Biogen retains overall accountability for these activities.

2. LIST OF ABBREVIATIONS

12F6A	recombinant, human anti-β-amyloid immunoglobulin G_1 monoclonal antibody with an amino acid sequence identical to aducanumab, produced in a different Chinese hamster ovary cell line
Aβ	β-amyloid (peptide derived from membrane bound amyloid precursor protein)
AA	Alzheimer's Association
AD	Alzheimer's disease
ADA	antidrug antibody
ADAS-Cog 13	Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items)
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment version)
AE	adverse event
ALT	alanine aminotransferase
ApoE	apolipoprotein E
ApoE ε4	apolipoprotein E4
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid-related imaging abnormality-edema
ARIA-H	amyloid-related imaging abnormality-hemorrhage or superficial siderosis
ASL-MRI	arterial spin labeling magnetic resonance imaging
AST	aspartate aminotransferase
CAM	Caregiver Assessment Measure
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating sum of boxes
ch12F6A	murine IgG_{2a} chimeric version of 12F6A or aducanumab
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	diastolic blood pressure
DHA	Directions for Handling and Administration
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
EDC	electronic data capture
EOT	End of Treatment
EQ-5D	EuroQol health status measure
EQ-5D (IR-I)	EuroQol health status measure, informant reported on

	informant's own health status
EQ-5D (IR-S)	EuroQol health status measure, informant reported on subject
EQ-5D (SR)	EuroQol health status measure, subject self-reported
FU	follow-up
GCP	Good Clinical Practice
HbA_{1c}	glycosylated hemoglobin
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HCP	health care professional
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
Ig	immunoglobulin
IR	informant rated
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous(ly)
IWG	International Working Group
LTE	long-term extension
LP	lumbar puncture
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-model repeated measures
MMSE	Mini-Mental State Examination
MOCA	Montreal Cognitive Assessment
mPDQ-20	Perceived Deficits Questionnaire-20 modified version
MRI	magnetic resonance imaging
NIA	National Institute on Aging
NIA-AA	National Institute on Aging (NIA) at National Institutes of Health (NIH) and the Alzheimer's Association (AA)
NPI-10	Neuropsychiatric Inventory-10
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic(s)
PET	positron emission tomography
PI	Principal Investigator
PK	pharmacokinetic(s)
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
RNA	ribonucleic acid
SABR	Safety and Benefit-Risk

SAE	serious adverse event
SAP	statistical analysis plan
SB	sum of boxes
SBP	systolic blood pressure
SD	standard deviation
SR	subject rated
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
tf-fMRI	task-free functional MRI

3. SYNOPSIS

Protocol Number:	**221AD301**
Protocol Title:	A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease
Version Number:	6.0
Name of Study Treatment:	Aducanumab (BIIB037)
Study Indication:	Alzheimer's Disease
Study Rationale:	The purpose of this Phase 3 study is to assess the efficacy and safety of aducanumab compared with placebo in subjects with early Alzheimer's Disease (AD), including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD. Aducanumab is a human monoclonal antibody that recognizes aggregated forms of β-amyloid (Aβ), including soluble Aβ oligomers and deposited fibrillar Aβ. Interim analyses of the ongoing multiple dose study (Study 221AD103) have demonstrated target engagement, a pharmacodynamic effect on amyloid reduction, and an effect on the Clinical Dementia Rating (CDR)-sum of boxes (SB) and Mini-Mental State Examination (MMSE) suggestive of a reduction in the progression of clinical impairment for aducanumab-treated subjects. These results, along with the observed safety and tolerability profile, warrant further Phase 3 investigation of aducanumab in a patient population spanning the early stages of the AD continuum.
Phase of Development:	3
Study Objectives and Endpoints (placebo-controlled period of the study):	The primary objective of the study is to evaluate the efficacy of monthly doses of aducanumab in slowing cognitive and functional impairment as measured by changes in the CDR-SB score as compared with placebo in subjects with early AD. The primary endpoint that relates to this objective is the change from baseline in CDR-SB score at Week 78. Secondary objectives and endpoints are as follows: To assess the effect of monthly doses of aducanumab as

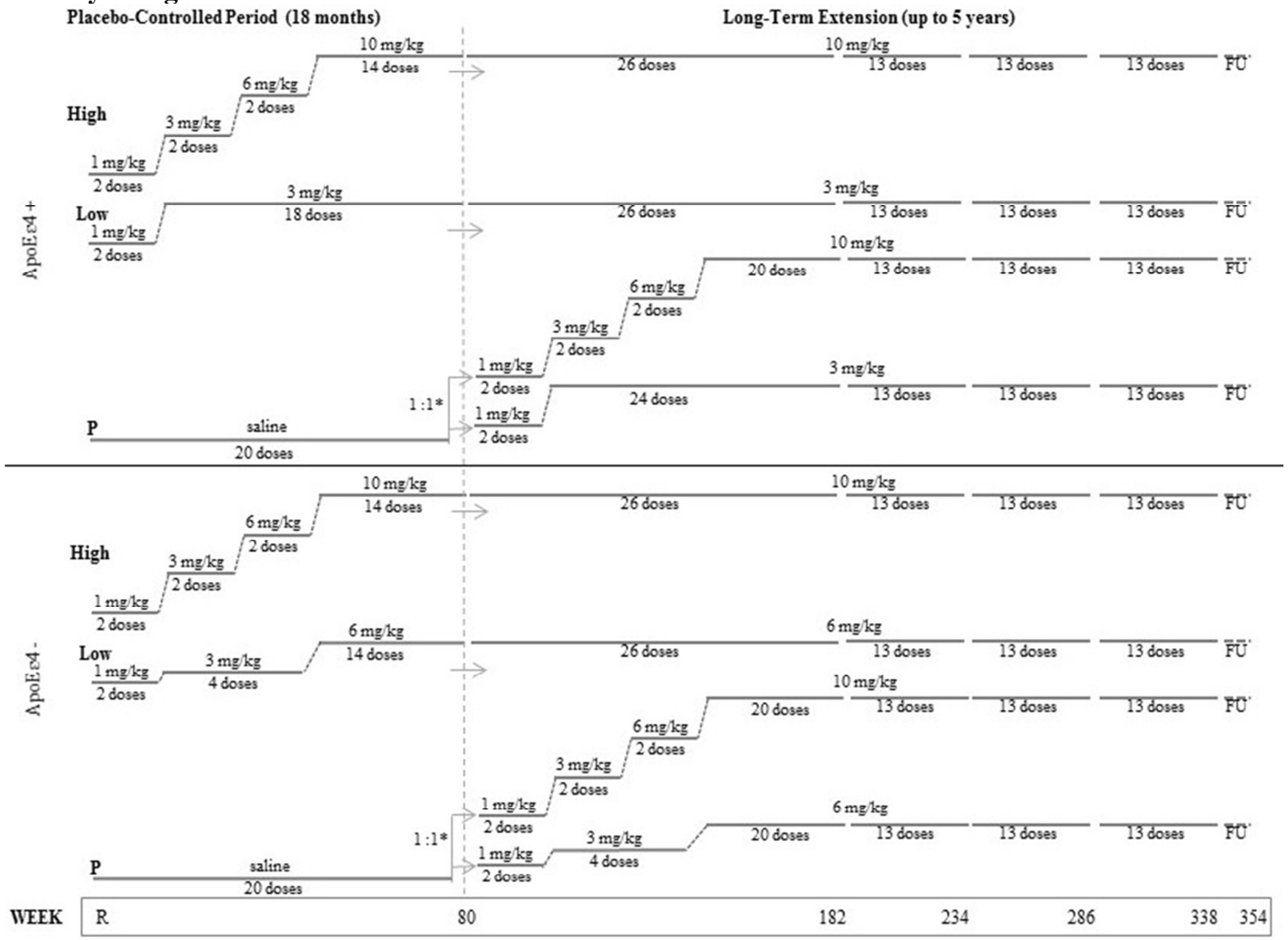
Protocol Number:	**221AD301**
	compared with placebo on clinical progression as measured by • MMSE - Change from baseline in MMSE score at Week 78 • Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13] - Change from baseline in ADAS-Cog 13 at Week 78 • Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI] - Change from baseline in ADCS-ADL-MCI score at Week 78 Tertiary objectives of this study are listed in Section 6.3.1. Tertiary endpoints of this study are listed in Section 6.3.2. Additional exploratory objectives and endpoints are listed in Section 6.4.
Study Objectives and Endpoints (Dose-Blind Long-Term Extension period of the study):	The objectives are to evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD, and to evaluate the long-term efficacy of aducanumab treatment as measured by clinical, radiological, and health-outcomes assessments. Endpoints for the long-term extension (LTE) period of the study are listed in Section 6.5.
Study Design:	Multicenter, randomized study with an 18-month double-blind, placebo-controlled, parallel-group period followed by an optional up to 5-year, dose-blind, LTE period
Study Location:	Approximately 150 sites globally
Number of Planned Subjects:	Approximately 1605 subjects are planned to be enrolled.
Study Population:	This study will be conducted in subjects with early AD, including subjects with MCI due to AD and a subset of mild AD according to National Institute on Aging (NIA) at the National Institutes of Health (NIH) and the Alzheimer's Association (NIA-AA) criteria. Subjects must be positive for amyloid pathology as measured by amyloid positron emission tomography scan. Subjects must be 50 to 85 years old, and apart from the clinical diagnosis of early AD, they must be in good health as determined by the Investigator, based on medical history and the screening assessments. The

Protocol Number:	**221AD301**
	ratio of apolipoprotein E4 (ApoE ε4) carriers to non-carriers in the study population will generally reflect the distribution in the broader AD population. Enrollment will also be monitored, via interactive response technology, such that subjects with mild AD represent a small percentage of the total enrolled in the trial. Detailed criteria are described in Section 8.
Treatment Groups:	For the 18-month placebo-controlled period of the study and based upon their ApoE ε4 carrier status, subjects will be assigned to 1 of 3 treatment groups in a 1:1:1 ratio (aducanumab low dose: aducanumab high dose:placebo) as follows: **ApoE ε4 carrier** **Low dose (3 mg/kg)** **High dose (10 mg/kg)** **Placebo** **ApoE ε4 non-carrier** **Low dose (6 mg/kg)** **High dose (10 mg/kg)** **Placebo** After completion of the placebo-controlled period, subjects may enter a dose-blind LTE study during which all subjects will receive aducanumab for up to 5 years.
Duration of Treatment and Follow Up:	Study duration for each subject participating in the placebo-controlled period only will be approximately 102 weeks (up to an 8-week screening period, 76 weeks of placebo or aducanumab dosing, and 18 weeks of follow-up [FU]). For subjects who enter the optional LTE period, the total study duration will vary and be up to approximately 362 weeks or 83 months (up to an 8-week screening period, 76 weeks of placebo or aducanumab dosing, and 4 weeks of FU, plus an optional LTE period including 256 weeks of dose-blind aducanumab dosing and 18 weeks of FU).

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY 221AD301

4.1. Study Schematic

Figure 1: Study Design



ApoE ε4 +/- = apolipoprotein E4 positive/negative; FU = follow-up; P = placebo; R = randomization date.

*Subjects who are assigned to placebo during the placebo-controlled period are randomized in a 1:1 ratio to high and low dose aducanumab treatment (based upon their ApoE ε4 carrier status) for the long-term extension period on Study Day 1.

4.2. Schedule of Events

Table 1: Placebo-Controlled Period Schedule From Screening Through Week 48

Study Week																		
	Screening (≤ 60 days before Day 1)[1]			**Wk 1, Day 1**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**UV for a Change in AD Medication**
Study Day	**V1**	**V2**	**V3**	**1**	**29 ± 3**	**57 ± 3**	**85 ± 3**	**113 ± 3**	**141 ± 3**	**169 ± 3**	**183 ± 3**	**197 ± 3**	**225 ± 3**	**253 ± 3**	**281 ± 3**	**309 ± 3**	**337 ± 3**	
Initial Screening Consent[2] (optional)	X																	
Full Informed Consent[3]	X																	
Eligibility Criteria	X	X	X	X[4]														
Demography	X																	
Medical History	X	X	X															
Alcohol/Drug Screen	X																	
HbA_{1c}	X																	
HIV[5]/Hepatitis/ Coagulation	X																	
ApoE Genotyping	X																	
DNA (optional)[6]	X																	
Height	X																	
Body Weight	X			X	X	X	X	X	X	X		X	X	X	X	X	X	
Serum Pregnancy Test[7]	X																	
Urine Pregnancy Test[7]				X	X	X	X	X	X	X		X	X	X	X	X	X	
Physical Examination	X						X			X							X	

Study Week																		
	Screening (≤ 60 days before Day 1)[1]			**Wk 1, Day 1**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**UV for a Change in AD Medication**
Study Day	**V1**	**V2**	**V3**	**1**	**29 ± 3**	**57 ± 3**	**85 ± 3**	**113 ± 3**	**141 ± 3**	**169 ± 3**	**183 ± 3**	**197 ± 3**	**225 ± 3**	**253 ± 3**	**281 ± 3**	**309 ± 3**	**337 ± 3**	
Neurological Examination	X						X			X							X	
12-lead Paper ECG	X									X							X	
Vital Signs[8]	X			X	X	X	X	X	X	X		X	X	X	X	X	X	
Hematology, Blood Chemistry and Urinalysis	X			X						X							X	
Randomization				X[9]														
Study Drug Infusion				X	X	X	X	X	X	X		X	X	X	X	X	X	
Anti-Aducanumab Ab[10]				X						X			X					
Aducanumab Concentration[11]				X[12]	X[12]		X[12]	X	X[12]	X[12]		X[12]	X					
RNA, Serum, and Plasma for Biomarkers[13]	X						X	X		X			X					
PBMC Collection	X						X	X		X			X					
CSF Collection (optional)	X[14]																	
Amyloid PET[15]			X								X							
Tau PET[16]			X															
RBANS	X																	
CDR	X										X							X

Study Week																		
	Screening (≤ 60 days before Day 1)[1]			**Wk 1, Day 1**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**UV for a Change in AD Medica-tion**
Study Day	**V1**	**V2**	**V3**	**1**	**29 ± 3**	**57 ± 3**	**85 ± 3**	**113 ± 3**	**141 ± 3**	**169 ± 3**	**183 ± 3**	**197 ± 3**	**225 ± 3**	**253 ± 3**	**281 ± 3**	**309 ± 3**	**337 ± 3**	
MMSE	X										X							X
ADCS-ADL-MCI		X[17]									X							X
ADAS-Cog 13		X[17]									X							X
NPI-10		X[18]									X							
EQ-5D (SR)		X[19]									X							
EQ-5D (IR-S)		X[19]									X							
EQ-5D (IR-I)		X[19]									X							
mPDQ-20		X[19]									X							
CAM		X[19]									X							
C-SSRS				X							X							
AE Reporting				Monitor and record continuously throughout the study														
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study																	
SAE Reporting	Monitor and record continuously throughout the study																	

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version); ApoE = apolipoprotein E; ARIA = amyloid-related imaging abnormalities; CAM = Caregiver Assessment Measure; CDR = Clinical Dementia Rating scale; CRO = contract research organization; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) = EQ-5D, subject self-reported; HbA1c = glycosylated hemoglobin; HIV = human immunodeficiency virus; LTE = long-term extension; MMSE = Mini Mental State Examination; mPDQ-20 = modified Perceived Deficits Questionnaire-20; MRI = magnetic resonance imaging; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; RBANS = Repeatable

Battery for the Assessment of Neuropsychological Status; RNA = ribonucleic acid; SAE = serious adverse event; UV = unscheduled visit; V1, V2, V3 = Screening Visit 1, Screening Visit 2, and Screening Visit 3; Wk = Week.

[1] Examination required for assessment of subject eligibility must be performed at V1. Brain MRI (Table 3) should only be performed once the subject meets eligibility criteria at V1. Amyloid PET should only be performed if the subject meets eligibility criteria at V1 and V2. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.

[2] Subjects may sign this optional form for an initial Screening which allows administration of the RBANS, CDR, and MMSE only, as well as ApoE genotyping.

[3] All subjects must sign this informed consent, including subjects who have signed the optional initial screening consent, once they have met the RBANS, CDR, and MMSE eligibility criteria.

[4] All assessments, including the C-SSRS, must be completed before study treatment administration, except the post-dose sample to measure aducanumab concentration.

[5] HIV testing is at the Investigator's discretion after consideration of risk factors.

[6] Can be collected at any point during and after Screening.

[7] Required for women of childbearing potential only (see Section 15.5).

[8] Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes.

[9] Randomization for both the placebo-controlled period and LTE period will occur on Study Day 1 (see Section 9.2).

[10] Sample collection for anti-aducanumab antibody will be performed prior to study treatment infusion (where applicable).

[11] Blood sampling for aducanumab concentration will be performed prior to infusion

[12] One additional blood sample for aducanumab concentration will be collected between 10 and 60 minutes after completion of the infusion and line flush. Note: For subjects who suspend treatment due to ARIA, only 1 blood sample is required to be collected at each specified visit during the period of dose suspension; all other visits/assessments are required to be performed.

[13] Samples will be collected prior to infusion (where applicable).

[14] May be collected at any point in time during Screening after eligibility at V1 is confirmed but if collected on the same day as an MRI, it should be collected after the MRI is performed. CSF collection at Screening using study-specific procedures is preferred; however, if a CSF sample has been obtained within 3 months prior to Screening, this sample may be used in lieu of requiring that the subject undergo a lumbar puncture at Screening.

[15] Screening amyloid PET is required for all subjects; amyloid PET at Week 26 will only be conducted in selected sites for subjects who are participating in the amyloid PET substudy. The amyloid PET at Week 26 may be scheduled within a window of ±7 days.

[16] Tau PET substudy may be performed in a subset of subjects at selected sites. Baseline tau PET scan must be done during the screening period, after confirmation of amyloid burden by the central imaging CRO (post-Screening V3) but prior to randomization. The screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.

[17] Must be performed within 20 days of V1, but not on the same day as the screening RBANS, CDR, or MMSE.

[18] The NPI-10 can be performed at any time during Screening as long as it is performed after the CDR (e.g., including at Screening V1).

[19] May be performed at any point during Screening after the subject has met eligibility criteria on the RBANS, CDR, and MMSE.

Table 2: Placebo-Controlled Period Schedule From Week 50 to End of Treatment or Follow-Up

Study Week											**FU**[1]
	50	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**78 (EOT)**[2]	**UV for a Change in AD Medication**	**94 (or 18 wks after final dose for subjects who DCT early)**
Study Day	**351 ± 3**	**365 ± 3**	**393 ± 3**	**421 ± 3**	**449 ± 3**	**477 ± 3**	**505 ± 3**	**533 ± 3**	**547 ± 3**		**659 ± 7**
Informed Consent									X[3]		
Eligibility Criteria									X[3]		
Body Weight		X	X	X	X	X	X	X			X
Urine Pregnancy Test[4]		X	X	X	X	X	X	X			X
Physical Examination							X		X		X
Neurological Examination							X		X		X
12-lead Paper ECG							X		X		X
Vital Signs[5]		X	X	X	X	X	X	X			X
Hematology, Blood Chemistry and Urinalysis							X		X		X
Study Treatment Infusion		X	X	X	X	X	X	X			

Study Week											**FU**[1]
	50	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**78 (EOT)**[2]	**UV for a Change in AD Medication**	**94 (or 18 wks after final dose for subjects who DCT early)**
Study Day	**351 ± 3**	**365 ± 3**	**393 ± 3**	**421 ± 3**	**449 ± 3**	**477 ± 3**	**505 ± 3**	**533 ± 3**	**547 ± 3**		**659 ± 7**
Anti-Aducanumab Ab[6]			X						X		X
Aducanumab Concentration[7]		X[8]	X						X		X
RNA, Serum, and Plasma for Biomarkers[9]			X						X		X
PBMC Collection			X						X		X
CSF Collection (optional)									X		
Amyloid PET[10]									X		
Tau PET[11]									X		
CDR	X								X	X	X
MMSE	X								X	X	X
ADCS-ADL MCI	X								X	X	X
ADAS-Cog 13	X								X	X	X
NPI-10	X								X		
EQ-5D (SR)	X								X		

Study Week											**FU**[1]
	50	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**78 (EOT)**[2]	**UV for a Change in AD Medication**	**94 (or 18 wks after final dose for subjects who DCT early)**
Study Day	**351 ± 3**	**365 ± 3**	**393 ± 3**	**421 ± 3**	**449 ± 3**	**477 ± 3**	**505 ± 3**	**533 ± 3**	**547 ± 3**		**659 ± 7**
EQ-5D (IR-S)	X								X		
EQ-5D (IR-I)	X								X		
mPDQ-20	X								X		
CAM	X								X		
C-SSRS		X							X		
AE Reporting	Monitor and record continuously throughout the study										
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study										
SAE Reporting	Monitor and record continuously throughout the study										

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version); ARIA = amyloid-related imaging abnormalities; CAM = Caregiver Assessment Measure; CDR = Clinical Dementia Rating scale; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; DCT = discontinue treatment; ECG = electrocardiogram; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) = EQ-5D, subject self-reported; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MMSE = Mini Mental State Examination; mPDQ-20 = modified Perceived Deficits Questionnaire-20; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; RNA = ribonucleic acid; SAE = serious adverse event; UV = unscheduled visit; wks = weeks.

[1] Subjects who complete the placebo-controlled period and do not enter the LTE are to return to the site for a safety FU Visit at Week 94. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose.

[2] Subjects who discontinue treatment prematurely are to remain in the study, attend a FU Visit 18 weeks after the final dose, and immediately continue protocol-required tests and assessments at a subset of the clinic visits (see Table 10, and Table 11) until the end of the study per the schedule of events. (It is possible that a clinic visit will occur before the FU Visit.) If the FU Visit will occur within 2 weeks of a scheduled clinic visit, then the FU Visit can be combined with the scheduled visit and all assessments required for both visits performed at this single visit. Note: Subjects who withdraw from study prematurely are to return to the site for an EOT Visit; for such subjects, efficacy assessments specified at the EOT visit are not required if the subject

discontinues treatment within 3 months of the previous efficacy assessment visit and no significant changes in cognitive status are suspected by the Investigator. The site should notify the Sponsor in such cases.

[3] Only for subjects entering the long-term extension period.

[4] Required for women of childbearing potential only (see Section 15.5).

[5] Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes.

[6] Sample collection for anti-aducanumab antibody will be performed prior to study treatment infusion (where applicable).

[7] Blood sampling for aducanumab concentration will be performed prior to infusion.

[8] One additional blood sample for aducanumab concentration will be collected between 10 and 60 minutes after completion of the infusion and line flush. Note: For subjects who suspend treatment due to ARIA, only 1 blood sample is required to be collected at each specified visit during the period of dose suspension; all other visits/assessments are required to be performed.

[9] Sample will be collected prior to infusion (where applicable).

[10] Amyloid PET at Week 78 will only be conducted in selected sites for subjects who are participating in the amyloid PET substudy and may be scheduled within a window of ±7 days.

[11] Tau PET substudy may be performed in a subset of subjects at selected sites and may be scheduled within a window of ±7 days. Serial follow-up tau PET scans will be performed after amyloid PET for those subjects also participating in the amyloid PET substudy, but may not be performed on the same day.

Table 3: Brain MRI, ARIA Management, and Follow-Up Phone Call Schedule During the Placebo-Controlled Period

Study Week	**Screening (≤ 60 days before Day 1)**[1]			**Placebo-Controlled Period**												**FU**[2]
				1	**2**	**6**	**10**	**14**	**18**	**22**	**26**	**30**	**42**	**54**	**66**	**78/ EOT**[3]	**Unsched-uled Visit/ MRI for ARIA**[4]	**94 (or 18 wks after final dose for subjects who DCT early)**
Study Day	**V1**	**V2**	**V3**	**1**	**15 ± 3**	**43 ± 3**	**71 ± 3**	**99 ± 3**	**127 ± 3**	**155 ± 3**	**183 ± 3**	**211 ± 3**	**295 ± 3**	**379 ± 3**	**463 ± 3**	**547 ± 3**		**659 ± 7**
Follow-Up Phone Call[5]					X	X	X	X	X	X	X	X						
Brain MRI[6]		X						X		X		X	X	X	X	X	X	X
Aducanumab Concentration[7]										X		X		X			X	X
MOCA				X													X	
RNA, Serum, and Plasma for Biomarkers[8]																	X	
PBMC Collection[8]																	X	

ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality-hemorrhage or superficial siderosis; DCT = discontinue treatment; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; RNA = ribonucleic acid; V1, V2, V3 = Screening Visit 1, Screening Visit 2, and Screening Visit 3; wks = weeks.

1 Brain MRI (V2) will not be performed until the subject has met the eligibility criteria and has acceptable laboratory tests from V1. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.

2 Subjects who complete the placebo-controlled period and do not enter the LTE are to return to the site for a safety FU Visit at Week 94. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose.

3 Subjects who discontinue treatment prematurely are to remain in the study, attend a FU Visit 18 weeks after the final dose, and immediately continue protocol-required tests and assessments at a subset of the clinic visits (see Table 10, and Table 11) until the end of the study per the schedule of events. (It is possible that a clinic visit will occur before the FU Visit.) If the FU Visit will occur within 2 weeks of a scheduled clinic visit, then the FU Visit can be combined with the scheduled visit and all assessments required for both visits performed at this single visit. Subjects who withdraw from study prematurely are

to return to the site for an EOT Visit; for such subjects, efficacy assessments specified at the EOT visit are not required if the subject discontinues treatment within 3 months of the previous efficacy assessment visit and no significant changes in cognitive status are suspected by the Investigator; The site should notify the sponsor in such cases.

[4] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[5] Phone visit may be performed in person if the subject will be at the study site for clinical assessments.

[6] Arterial spin labeling MRI and task-free functional MRI will be performed only at a subset of sites.

[7] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

[8] Sample may be collected ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

Table 4: Long-Term Extension Period Schedule From Week 80 to Week 134

Study Week																	
	80	**84**	**88**	**92**	**96**	**100**	**104**	**106**	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**134**	**UV for a Change in AD Medica-tion**
Study Day	**561 ± 5**	**589 ± 5**	**617 ± 5**	**645 ± 5**	**673 ± 5**	**701 ± 5**	**729 ± 5**	**743 ± 5**	**757 ± 5**	**785 ± 5**	**813 ± 5**	**841 ± 5**	**869 ± 5**	**897 ± 5**	**925 ± 5**	**939 ± 5**	
Body Weight	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Urine Pregnancy Test[1]	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Physical Examination				X			X							X			
Neurological Examination				X			X							X			
12-lead Paper ECG							X							X			
Vital Signs	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Hematology, Blood Chemistry and Urinalysis							X							X			
Anti-Aducanumab Ab[2]	X						X							X			
RNA, Serum, and Plasma for Biomarkers[2]							X							X			
PBMC Collection							X							X			
Aducanumab Concentration[2]	X						X							X			

Study Week																	
	80	**84**	**88**	**92**	**96**	**100**	**104**	**106**	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**134**	**UV for a Change in AD Medica-tion**
Study Day	**561 ± 5**	**589 ± 5**	**617 ± 5**	**645 ± 5**	**673 ± 5**	**701 ± 5**	**729 ± 5**	**743 ± 5**	**757 ± 5**	**785 ± 5**	**813 ± 5**	**841 ± 5**	**869 ± 5**	**897 ± 5**	**925 ± 5**	**939 ± 5**	
Study Treatment Infusion	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
CSF Collection (optional)[3]															X		
Amyloid PET[4]															X		
Tau PET[5]															X		
CDR								X								X	X
MMSE								X								X	X
ADAS-Cog 13								X								X	X
ADCS-ADL-MCI								X								X	X
NPI-10								X								X	
EQ-5D (IR-S)								X								X	
EQ-5D (IR-I)								X								X	
CAM								X								X	
C-SSRS								X								X	
AE Reporting	Monitor and record continuously throughout the study																
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study																
SAE Reporting	Monitor and record continuously throughout the study																

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); CAM = Caregiver Assessment Measure; CDR = Clinical Dementia Rating; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; LTE = long-term extension; MMSE = Mini-Mental State Examination; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; RNA = ribonucleic acid; SAE = serious adverse event; UV = unscheduled visit.

[1] Required for women of childbearing potential only (see Section 15.5).

[2] Sample will be collected prior to infusion (where applicable).

[3] Enrolled subjects who consented to CSF collection during the placebo-controlled period will have the option to consent to CSF collection during the first 2 years of the LTE period.

[4] Only for subjects who participate in the amyloid PET substudy. Amyloid PET may be scheduled within a window of ±7 days.

[5] Tau PET substudy may be conducted at selected sites and may be scheduled within a window of ±7 days. Serial follow-up tau PET scans will be performed after amyloid PET scan for those subjects also participating in the amyloid PET substudy, but may not be performed on the same day.

Table 5: Long-Term Extension Period Schedule From Week 136 to Week 182

Study Week															
	136	**140**	**144**	**148**	**152**	**156**	**160**	**162**	**164**	**168**	**172**	**176**	**180**	**182**	**UV for a Change in AD Medication**
Study Day	**953 ± 5**	**981 ± 5**	**1009 ± 5**	**1037 ± 5**	**1065 ± 5**	**1093 ± 5**	**1121 ± 5**	**1135 ± 5**	**1149 ± 5**	**1177 ± 5**	**1205 ± 5**	**1233 ± 5**	**1261 ± 5**	**1275 ± 5**	
Body Weight	X	X	X	X	X	X	X		X	X	X	X	X	X	
Urine Pregnancy Test[1]	X	X	X	X	X	X	X		X	X	X	X	X	X	
Physical Examination					X							X		X	
Neurological Examination					X							X		X	
12-lead Paper ECG					X							X			
Vital Signs	X	X	X	X	X	X	X		X	X	X	X	X	X	
Hematology, Blood Chemistry and Urinalysis					X							X			
Anti-Aducanumab Ab[2]					X									X	
RNA, Serum, and Plasma for Biomarkers[2]					X									X	
PBMC Collection					X									X	
Aducanumab Concentration[2]					X							X		X	
Study Drug Infusion	X	X	X	X	X	X	X		X	X	X	X	X		
CSF Collection (optional)[3]														X	
Amyloid PET[4]														X	

Study Week															
	136	**140**	**144**	**148**	**152**	**156**	**160**	**162**	**164**	**168**	**172**	**176**	**180**	**182**	**UV for a Change in AD Medication**
Study Day	**953 ± 5**	**981 ± 5**	**1009 ± 5**	**1037 ± 5**	**1065 ± 5**	**1093 ± 5**	**1121 ± 5**	**1135 ± 5**	**1149 ± 5**	**1177 ± 5**	**1205 ± 5**	**1233 ± 5**	**1261 ± 5**	**1275 ± 5**	
Tau PET[5]														X	
CDR								X						X	X
MMSE								X						X	X
ADAS-Cog 13								X						X	X
ADCS-ADL-MCI								X						X	X
NPI-10								X						X	
EQ-5D (IR-S)								X						X	
EQ-5D (IR-I)								X						X	
CAM								X						X	
C-SSRS								X						X	
AE Reporting	Monitor and record continuously throughout the study														
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study														
SAE Reporting	Monitor and record continuously throughout the study														

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); CAM = Caregiver Assessment Measure; CDR = Clinical Dementia Rating; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MMSE = Mini-Mental State Examination; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; RNA = ribonucleic acid; SAE = serious adverse event; UV = unscheduled visit.

[1] Required for women of childbearing potential only (Section 15.5).

[2] Sample will be collected prior to infusion (where applicable).

[3] Enrolled subjects who consented to CSF collection during the placebo-controlled period will have the option to consent to CSF collection during the first 2 years of the LTE period.

[4] Only for subjects who participate in the amyloid PET substudy. Amyloid PET may be scheduled within a window of ±7 days.

[5] Tau PET substudy may be conducted at selected sites and may be scheduled within a window of ±7 days. Serial follow-up tau PET scans will be performed after amyloid PET for those subjects also participating in the amyloid PET substudy, but may not be performed on the same day.

Table 6: Brain MRI, ARIA Management, and Follow-Up Phone Call Schedule From Weeks 80 to 182 of the Long-Term Extension Period

Study Week	**Long-Term Extension**													**Unscheduled Visit for ARIA**[1]
	80	**82**	**86**	**90**	**94**	**98**	**102**	**106**	**110**	**122**	**134**	**158**	**182**	
Study Day	**561 ± 5**	**575 ± 5**	**603 ± 5**	**631 ± 5**	**659 ± 5**	**687 ± 5**	**715 ± 5**	**743 ± 5**	**771 ± 5**	**855 ± 5**	**939 ± 5**	**1107 ± 5**	**1275 ± 5**	
Follow-Up Phone Call[2]		X	X	X	X	X	X	X	X					
Brain MRI[3]					X		X		X	X	X	X	X	X[3]
Aducanumab Concentration[4]														X
MOCA	X													X
RNA, Serum, and Plasma for Biomarkers[5]														X
PBMC Collection[5]														X

ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality-hemorrhage or superficial siderosis; EOT = End of Treatment; LTE = long-term extension; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; RNA = ribonucleic acid.

[1] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[2] Phone visit may be performed in person if the subject will be at the study site for clinical assessments.

[3] Arterial-spin labeling MRI and task-free functional MRI will be performed only at a subset of sites, and will not be performed at any visit after Week 182.

[4] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

[5] Sample may be collected within ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

Table 7: Long-Term Extension Period Schedule From Week 184 to Week 234

Study Week														
	184	**188**	**192**	**196**	**200**	**204**	**208**	**212**	**216**	**220**	**224**	**228**	**232**	**UV for ARIA**[1]
Study Day	**1289 ± 5**	**1317 ± 5**	**1345 ± 5**	**1373 ± 5**	**1401 ± 5**	**1429 ± 5**	**1457 ± 5**	**1485 ± 5**	**1513 ± 5**	**1541 ± 5**	**1569 ± 5**	**1597 ± 5**	**1625 ± 5**	
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine Pregnancy Test[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination							X						X	
Neurological Examination							X						X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology, Blood Chemistry and Urinalysis													X	
RNA, Serum, and Plasma for Biomarkers														X[3]
PBMC Collection														X[3]
Aducanumab Concentration														X[4]
Study Treatment Infusion	X	X	X	X	X	X	X	X	X	X	X	X	X	
Brain MRI													X	X
CDR													X	
MMSE													X	
ADAS-Cog 13													X	
ADCS-ADL-MCI													X	
EQ-5D-(IR-S)													X	
EQ-5D-(IR-I)													X	

Study Week														
	184	**188**	**192**	**196**	**200**	**204**	**208**	**212**	**216**	**220**	**224**	**228**	**232**	**UV for ARIA**[1]
Study Day	**1289 ± 5**	**1317 ± 5**	**1345 ± 5**	**1373 ± 5**	**1401 ± 5**	**1429 ± 5**	**1457 ± 5**	**1485 ± 5**	**1513 ± 5**	**1541 ± 5**	**1569 ± 5**	**1597 ± 5**	**1625 ± 5**	
MOCA														X
C-SSRS													X	
AE Reporting	Monitor and record continuously throughout the study													
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study													
SAE Reporting	Monitor and record continuously throughout the study													

AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version); ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality hemorrhage or superficial siderosis; CDR = Clinical Dementia Rating scale; C-SSRS = Columbia Suicide Severity Rating Scale; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; LTE = long-term extension; MMSE = Mini Mental State Examination; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; RNA = ribonucleic acid; SAE = serious adverse event; UV = unscheduled visit.

[1] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[2] Required for women of childbearing potential only (Section 15.5).

[3] Sample may be collected within ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

[4] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

Table 8: Long-Term Extension Period Schedule From Week 236 to Week 286

Study Week														
	236	**240**	**244**	**248**	**252**	**256**	**260**	**264**	**268**	**272**	**276**	**280**	**284**	**UV for ARIA**[1]
Study Day	**1653 ± 5**	**1681 ± 5**	**1709 ± 5**	**1737 ± 5**	**1765 ± 5**	**1793 ± 5**	**1821 ± 5**	**1849 ± 5**	**1877 ± 5**	**1905 ± 5**	**1933 ± 5**	**1961 ± 5**	**1989 ± 5**	
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine Pregnancy Test[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination							X						X	
Neurological Examination							X						X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology, Blood Chemistry and Urinalysis													X	
RNA, Serum, and Plasma for Biomarkers														X[3]
PBMC Collection														X[3]
Aducanumab Concentration														X[4]
Study Treatment Infusion	X	X	X	X	X	X	X	X	X	X	X	X	X	
Brain MRI													X	X
Amyloid PET[5]							X							
CDR													X	
MMSE													X	
ADAS-Cog 13													X	
ADCS-ADL-MCI													X	
EQ-5D-(IR-S)													X	

Study Week														
	236	**240**	**244**	**248**	**252**	**256**	**260**	**264**	**268**	**272**	**276**	**280**	**284**	**UV for ARIA**[1]
Study Day	**1653 ± 5**	**1681 ± 5**	**1709 ± 5**	**1737 ± 5**	**1765 ± 5**	**1793 ± 5**	**1821 ± 5**	**1849 ± 5**	**1877 ± 5**	**1905 ± 5**	**1933 ± 5**	**1961 ± 5**	**1989 ± 5**	
EQ-5D-(IR-I)													X	
MOCA														X
C-SSRS													X	
AE Reporting	Monitor and record continuously throughout the study													
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study													
SAE Reporting	Monitor and record continuously throughout the study													

AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version); ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality hemorrhage or superficial siderosis; CDR = Clinical Dementia Rating scale; C-SSRS = Columbia Suicide Severity Rating Scale; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; LTE = long-term extension; MMSE = Mini Mental State Examination; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; PK = pharmacokinetic; RNA = ribonucleic acid; SAE = serious adverse event; UV = unscheduled visit.

[1] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[2] Required for women of childbearing potential only (Section 15.5).

[3] Sample may be collected within ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

[4] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

[5] Only for subjects who participate in the amyloid PET substudy. Amyloid PET may be scheduled within a window of ±7 days.

Table 9: Long-Term Extension Period Schedule From Week 288 to the End of Treatment or Follow-Up

Study Week																**FU**[1]
	288	**292**	**296**	**300**	**304**	**308**	**312**	**316**	**320**	**324**	**328**	**332**	**336**	**338 EOT**[2]	**UV for ARIA**[3]	**354 (or 18 wks after final dose for subjects who DCT early)**
Study Day	**2017 ± 5**	**2045 ± 5**	**2073 ± 5**	**2101 ± 5**	**2129 ± 5**	**2157 ± 5**	**2185 ± 5**	**2213 ± 5**	**2241 ± 5**	**2269 ± 5**	**2297 ± 5**	**2325 ± 5**	**2353 ± 5**	**2367 ± 5**		**2479 ± 7**
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Urine Pregnancy Test[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Physical Examination							X							X		X
Neurological Examination							X							X		X
12-lead Paper ECG																X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Hematology, Blood Chemistry and Urinalysis													X			X
Anti-Aducanumab Ab														X		X
RNA, Serum, and Plasma for Biomarkers														X[5]	X[6]	X
PBMC Collection														X[5]	X[6]	X
Aducanumab Concentration														X	X[7]	X
Study Treatment Infusion	X	X	X	X	X	X	X	X	X	X	X	X	X			

Study Week																**FU**[1]
	288	**292**	**296**	**300**	**304**	**308**	**312**	**316**	**320**	**324**	**328**	**332**	**336**	**338 EOT**[2]	**UV for ARIA**[3]	**354 (or 18 wks after final dose for subjects who DCT early)**
Study Day	**2017 ± 5**	**2045 ± 5**	**2073 ± 5**	**2101 ± 5**	**2129 ± 5**	**2157 ± 5**	**2185 ± 5**	**2213 ± 5**	**2241 ± 5**	**2269 ± 5**	**2297 ± 5**	**2325 ± 5**	**2353 ± 5**	**2367 ± 5**		**2479 ± 7**
CSF Collection (optional, if collected at baseline)[8]														X[5]		
Brain MRI														X[9]	X	X[9]
Amyloid PET[10]														X		
Tau PET														X[11]		
CDR														X		X
MMSE														X		X
ADAS-Cog 13														X		X
ADCS-ADL-MCI														X		X
NPI-10														X[5]		
EQ-5D-(IR-S)														X		
EQ-5D-(IR-I)														X		
CAM														X[5]		
MOCA															X	
C-SSRS														X		
AE Reporting	Monitor and record continuously throughout the study															
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study															

Study Week																**FU**[1]
	288	**292**	**296**	**300**	**304**	**308**	**312**	**316**	**320**	**324**	**328**	**332**	**336**	**338 EOT**[2]	**UV for ARIA**[3]	**354 (or 18 wks after final dose for subjects who DCT early)**
Study Day	**2017 ± 5**	**2045 ± 5**	**2073 ± 5**	**2101 ± 5**	**2129 ± 5**	**2157 ± 5**	**2185 ± 5**	**2213 ± 5**	**2241 ± 5**	**2269 ± 5**	**2297 ± 5**	**2325 ± 5**	**2353 ± 5**	**2367 ± 5**		**2479 ± 7**
SAE Reporting	Monitor and record continuously throughout the study															

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version); ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality hemorrhage or superficial siderosis; CAM = Caregiver Assessment Measure; CDR = Clinical Dementia Rating scale; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; DCT = discontinue treatment; ECG = electrocardiogram; EOT = end of treatment; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; FU = follow-up ; LTE = long-term extension; MMSE = Mini Mental State Examination; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; PK = pharmacokinetic; RNA = ribonucleic acid; SAE = serious adverse event; UV = unscheduled visit; wks = weeks.

[1] Subjects who complete the LTE period are to return to the site for a safety FU Visit at Week 354. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose.

[2] Subjects who discontinue treatment prematurely are to remain in the study, attend a FU Visit 18 weeks after the final dose, and immediately continue protocol-required tests and assessments continue protocol-required tests and assessments at a subset of the clinic visits (see Table 11) until the end of the study per the schedule of events. (It is possible that a clinic visit will occur before the FU Visit.) If the FU Visit will occur within 2 weeks of a scheduled clinic visit, then the FU Visit can be combined with the scheduled visit and all assessments required for both visits performed at this single visit. Subjects who withdraw from study prematurely are to return to the site for an EOT Visit. For subjects who discontinue treatment early, efficacy assessments specified at the EOT visit are not required if the subject discontinues treatment within 3 months of the previous efficacy assessment visit and no significant changes in cognitive status are suspected by the Investigator. The site should notify the Sponsor in such cases.

[3] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[4] Required for women of childbearing potential only (see Section 15.5).

[5] This assessment is only to be performed if the EOT Visit is at or before Week 182.

[6] Sample may be collected within ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

[7] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.
[8] Enrolled subjects who consented to CSF collection during the placebo-controlled period will have the option to consent to CSF collection at the EOT Visit.
[9] Arterial-spin labeling MRI and task-free functional MRI will be performed only at a subset of sites, and will not be performed at any visit after Week 182.
[10] Only for subjects who participate in the amyloid PET substudy. Amyloid PET may be scheduled within a window of ±7 days.
[11] This assessment is only to be performed if the EOT Visit is at or before Week 182. Tau PET substudy may be conducted at selected sites and may be scheduled within a window of ±7 days. Serial follow-up tau PET scans will be performed after amyloid PET for those subjects also participating in the amyloid PET substudy, but may not be performed on the same day.

Table 10: Subjects Who Discontinue Study Treatment but Remain in the Study – Placebo-Controlled Period

Study Week	**Placebo-Controlled Period**[1]							
	12	**24**	**26**	**48**	**50**	**72**	**78 (EOT)**[2]	**UV for ARIA**[3]
Study Day	**85 ± 3**	**169 ± 3**	**183 ± 3**	**337 ± 3**	**351 ± 3**	**505± 3**	**547 ± 3**	
Informed Consent							X[4]	
Body Weight	X	X		X		X		
Eligibility Criteria							X[4]	
Physical Examination	X	X		X		X	X	
Neurological Examination	X	X		X		X	X	
12-lead Paper ECG		X		X		X	X	
Vital Signs	X	X		X		X		
Hematology, Blood Chemistry and Urinalysis		X		X		X	X	
RNA, Serum, and Plasma for Biomarkers	X	X					X	X[5]
PBMC Collection								X[5]
Aducanumab Concentration								X[6]
CSF Collection (optional)							X	
Brain MRI[7]							X	X
Amyloid PET[8]			X				X	
Tau PET[9]							X	
CDR			X		X		X	
MMSE			X		X		X	
ADAS-Cog 13			X		X		X	
ADCS-ADL-MCI			X		X		X	

Study Week	**Placebo-Controlled Period**[1]							
	12	**24**	**26**	**48**	**50**	**72**	**78 (EOT)**[2]	**UV for ARIA**[3]
Study Day	**85 ± 3**	**169 ± 3**	**183 ± 3**	**337 ± 3**	**351 ± 3**	**505± 3**	**547 ± 3**	
NPI-10			X		X		X	
EQ-5D (SR)			X		X		X	
EQ-5D (IR-S)			X		X		X	
EQ-5D (IR-I)			X		X		X	
mPDQ-20			X		X		X	
CAM			X		X		X	
MOCA								X
C-SSRS			X				X	
AE Reporting	Monitor and record continuously throughout the study							
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study							
SAE Reporting	Monitor and record continuously throughout the study							

AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version); ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality hemorrhage or superficial siderosis; CAM = Caregiver Assessment Measure; CDR = Clinical Dementia Rating scale; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOT = end of treatment; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) = EQ-5D, subject self-reported; FU = follow-up; LTE = long-term extension; MMSE = Mini Mental State Examination; mPDQ-20 = modified Perceived Deficits Questionnaire-20; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; PK = pharmacokinetic; RNA = ribonucleic acid; SAE = serious adverse event; SoE = schedule of events; UV = unscheduled visit.

[1] Subjects who discontinue study treatment prematurely during the placebo-controlled period are to remain in the study, attend a FU Visit 18 weeks after their final dose as listed in Table 2 and Table 3, and immediately continue protocol-required tests and assessments at a subset of the clinic visits (see Table 10, and Table 11) until the end of the study per the schedule of events. (It is possible that a clinic visit will occur before the FU Visit.) If the FU Visit will occur within 2 weeks of a scheduled clinic visit, then the FU Visit can be combined with the scheduled visit and all assessments required for both visits performed at this single visit. If the subject who discontinued treatment but remained in the study chooses to enroll in the LTE period, he or she will follow the SoE in Table 11.

[2] Subjects who withdraw from study prematurely are to return to the site for an EOT Visit; for such subjects, efficacy assessments specified at the EOT Visit are not required if the subject discontinues treatment within 3 months of the previous efficacy assessment visit and no significant changes in cognitive status are suspected by the Investigator. The site should notify the Sponsor in such cases.

[3] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[4] Only for subjects entering the long-term extension period.

[5] Sample may be collected within ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

[6] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

[7] Arterial spin labeling MRI and task-free functional MRI will be performed only at a subset of sites.

[8] Only for subjects who participate in the amyloid PET substudy. Amyloid PET may be scheduled within a window of ±7 days.

[9] Tau PET substudy may be conducted at selected sites and may be scheduled within a window of ±7 days. Serial follow-up tau PET scans will be performed after amyloid PET for those subjects also participating in the amyloid PET substudy, but may not be performed on the same day.

Table 11: Subjects Who Discontinue Study Treatment but Remain in the Study – Long-Term Extension Period

Study Week	**LTE Period**[1]															
	92	**104**	**106**	**128**	**134**	**152**	**162**	**176**	**182**	**208**	**232**	**260**	**284**	**312**	**338 (EOT)**[2]	**UV for ARIA**[3]
Study Day	**645 ± 5**	**729 ± 5**	**743 ± 5**	**897 ± 5**	**939 ± 5**	**1065 ± 5**	**1135 ± 5**	**1233 ± 5**	**1275 ± 5**	**1457 ± 5**	**1625 ± 5**	**1821 ± 5**	**1989 ± 5**	**2185 ± 5**	**2367 ± 5**	
Body Weight	X	X		X		X		X	X	X	X	X	X	X	X	
Physical Examination	X	X		X		X		X	X	X	X	X	X	X	X	
Neurological Examination	X	X		X		X		X	X	X	X	X	X	X	X	
12-lead Paper ECG		X		X		X		X								
Vital Signs	X	X		X		X		X	X	X	X	X	X	X	X	
Hematology, Blood Chemistry and Urinalysis		X		X		X		X			X		X			
RNA, Serum, and Plasma for Biomarkers		X		X		X			X						X[4]	X[5]
PBMC Collection																X[5]
Aducanumab Concentration																X[6]
CSF Collection (optional)									X						X[4]	
Brain MRI[7]					X				X		X		X		X[7]	X
Amyloid PET[8]									X			X			X	
Tau PET									X						X[9]	
CDR			X		X		X		X		X		X		X	
MMSE			X		X		X		X		X		X		X	
ADAS-Cog 13			X		X		X		X		X		X		X	
ADCS-ADL-MCI			X		X		X		X		X		X		X	
NPI-10			X		X		X		X						X[4]	

Study Week	**LTE Period**[1]															
	92	**104**	**106**	**128**	**134**	**152**	**162**	**176**	**182**	**208**	**232**	**260**	**284**	**312**	**338 (EOT)**[2]	**UV for ARIA**[3]
Study Day	**645 ± 5**	**729 ± 5**	**743 ± 5**	**897 ± 5**	**939 ± 5**	**1065 ± 5**	**1135 ± 5**	**1233 ± 5**	**1275 ± 5**	**1457 ± 5**	**1625 ± 5**	**1821 ± 5**	**1989 ± 5**	**2185 ± 5**	**2367 ± 5**	
EQ-5D-(IR-S)			X		X		X		X		X		X		X	
EQ-5D-(IR-I)			X		X		X		X		X		X		X	
CAM			X		X		X		X						X[4]	
MOCA																X
C-SSRS			X		X		X		X		X		X		X	
AE Reporting	Monitor and record continuously throughout the study															
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study															
SAE Reporting	Monitor and record continuously throughout the study															

AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version);ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality hemorrhage or superficial siderosis; CAM = Caregiver Assessment Measure; CDR = Clinical Dementia Rating scale; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOT = end of treatment; EQ-5D (IR-I) = EuroQol health status measure, informant reported on informant's own health status; EQ-5D (IR-S) = EQ-5D, informant reported on subject; FU = follow-up; LTE = long-term extension; MMSE = Mini Mental State Examination; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; NPI 10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; PK = pharmacokinetic; RNA = ribonucleic acid; SAE = serious adverse event; UV = unscheduled visit.

[1] Subjects who discontinue study treatment during the LTE period are to remain in the study, attend a FU Visit as listed in Table 9, and then will continue protocol-required tests and assessments at a subset of the clinic visits.

[2] Subjects who withdraw from study prematurely are to return to the site for an EOT Visit; for such subjects, efficacy assessments specified at the EOT Visit are not required if the subject discontinues treatment within 3 months of the previous efficacy assessment visit and no significant changes in cognitive status are suspected by the Investigator. The site should notify the Sponsor in such cases.

[3] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[4] This assessment is only to be performed if the EOT Visit is at or before Week 182.

[5] Sample may be collected within ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

[6] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.
[7] Arterial-spin labeling MRI and task-free functional MRI will be performed only at a subset of sites, and will not be performed at any visit after Week 182.
[8] Only for subjects who participate in the amyloid PET substudy. Amyloid PET may be scheduled within a window of ±7 days.
[9] This assessment is only to be performed if the EOT Visit is at or before Week 182. Tau PET substudy may be conducted at selected sites and may be scheduled within a window of ±7 days. Serial follow-up tau PET scans will be performed after amyloid PET for those subjects also participating in the amyloid PET substudy, but may not be performed on the same day.

4.3. Additional Information

4.3.1. Site Personnel

A minimum of 3 separate heath care professionals (HCPs) are required:

1. A treating HCP (the Principal Investigator [PI] or Sub-investigator may serve as a treating HCP) who is responsible for the following:
   - Administration of Montreal Cognitive Assessment (MOCA) at Day 1, Week 80, and during management of amyloid-related imaging abnormalities (ARIA) cases.
   - Management of routine neurological care of the subject.
   - Assessment (including assignment of causality) and treatment of adverse events (AEs).
   - Review of selected hematology and blood chemistry results from the central laboratory to assess if the subject's study treatment should be temporarily withheld or permanently discontinued according to the criteria detailed in Section 10.1.
2. An independent rating HCP (designated by the PI of the site) who is responsible for administering the Clinical Dementia Rating (CDR)
3. A second independent rating HCP (designated by the PI of the site) who will administer the Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13], Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI], and the Mini-Mental State Examination (MMSE)

The 2 independent rating HCPs must not be involved with any other aspect of subject care and management and must remain blinded to AEs, concomitant therapy, laboratory data, imaging data, or any other data that have the potential of revealing the treatment assignment. The 2 independent rating HCPs must not share any information about subjects. PIs cannot serve as rating HCPs. The treating HCPs must not discuss AEs (e.g., ARIA) with the independent rating HCPs.

To ensure consistency across sites, rating HCPs must complete the standardized study-specific qualification process on clinical efficacy assessment scoring prior to administration of the specific assessment at their site. All sites must attempt to maintain the same rating HCP throughout the study for specific assessments in an attempt to remain consistent. Each subject should have the same rating HCP perform the subject's specific rating assessment throughout the study. A qualified approved back-up rater should only conduct assessments in place of the primary rater due to extenuating circumstances resulting in unavailability (e.g., due to illness, vacation, or travel). If a rating HCP has to be replaced, the new rating HCP must undergo the study-specific qualification process prior to administration of the assessment.

Hematology and blood chemistry data will be sent to the investigational sites to aid in management of the subject. As with other laboratory and clinical information, these data should NOT be reviewed by the rating HCPs.

The roles of independent raters and treating HCP are NOT interchangeable at the subject level. In addition, the 2 independent raters are not interchangeable at the subject level. If a rater has administered the CDR to a subject, they may not administer the other neurocognitive assessments to that subject at any point during the study.

An unblinded pharmacist (or authorized designee) will be responsible for the storage, distribution, preparation, and accountability of study treatment. The unblinded pharmacist will also be responsible for maintaining the unblinded pharmacy record separate from the main study file in order to support the study blind.

5. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 50% to 75% of all cases. Alzheimer's Disease International estimates that as of 2013, there were 44.4 million people living with dementia worldwide and that this figure will increase to 135.5 million by 2050 [Alzheimer's Disease International 2014].

Clinically, AD is a progressive neurodegenerative disorder characterized by an insidious and unrelenting decline in cognition and behavioral disturbances that result in the person's inability to perform usual activities of daily living [Jack 2013].

Pathologically, AD is defined by the presence in the brain of extracellular neuritic plaques containing β-amyloid (Aβ) peptide and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau proteins. The pathogenesis of these plaques and tangles and how they contribute to the clinical syndrome remain to be fully elucidated, but the leading hypothesis — the "amyloid cascade"— proposes that the driving force behind the disease process is the accumulation of Aβ resulting from an imbalance between Aβ production and Aβ clearance in the brain [Hardy and Selkoe 2002].

The current view of AD, the disease process and its clinical manifestations, is that it manifests along a continuum rather than having categorical stages. Evidence suggests the pathophysiological changes begin years before clinical onset and as the disease progresses, cognitive impairments, behavioral changes, and functional disability manifest [Jack 2013]. Revised criteria for the clinical diagnosis of AD were published by the National Institute on Aging (NIA) at the National Institutes of Health (NIH) and the Alzheimer's Association (AA) [Albert 2011; McKhann 2011; Sperling 2011] and the International Working Group (IWG) [Dubois 2010; Dubois 2014], and a group that included members from both NIA-AA and IWG published recommendations to harmonize the criteria [Morris 2014]. These criteria base the diagnosis of AD on both clinical and biological elements, recognizing the existence of a nonclinical stage of the disease by accepting AD diagnoses prior to signs of dementia using AD biomarkers.

The scientific community has shifted its focus to target patients in the earlier course of the disease continuum with the belief that those patients are more likely to benefit from anti-amyloid therapy.

There are currently no therapies that modify the course of AD, but several potential disease-modifying drug candidates are under investigation. These candidates include small molecules and immunotherapy (active and passive) that target the Aβ pathway and aim to provide therapeutic benefit by reducing either soluble or insoluble forms of Aβ in the brain and cerebrospinal fluid (CSF). Aducanumab is a human monoclonal antibody that recognizes aggregated forms of Aβ, including soluble Aβ oligomers and deposited fibrillar Aβ. Earlier publications have reported on results that demonstrated in the brain of an animal model of AD that both soluble oligomers and amyloid plaques are neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008] and clearance of amyloid plaques could lead to normalization of calcium homeostasis and neuronal activity, as well as reduction of oxidative stress [Rozkalne

2009; Spires-Jones 2009]. Similarly, patients with AD who generated anti-Aβ antibodies after active immunization with aggregated Aβ(42) showed slower rates of decline of cognitive function and activities of daily living [Hock 2003].

5.1. Profile of Previous Experience With Aducanumab

5.1.1. Nonclinical Experience

Aducanumab is a unique human, anti-Aβ immunoglobulin (Ig) G1 monoclonal antibody identified and derived from B lymphocytes using the reverse translational medicine approach. Using this technique, immune repertoires obtained from cohorts of healthy elderly human donors with excellent cognitive performance or with impaired but stable courses were screened for memory B cells against aggregated Aβ.

In vitro studies have demonstrated that aducanumab and its analogs are highly selective for soluble oligomeric and insoluble fibrillar forms of Aβ relative to soluble low-molecular-weight forms of Aβ. In vivo pharmacology studies indicated that a murine IgG2a chimeric version of the antibody (ch12F6A) with similar properties to aducanumab (BIIB037) significantly reduced amyloid plaque burden in the brains of aged Tg2576 mice, a mouse model of AD, through a microglia-mediated phagocytic mechanism. These data suggest aducanumab could provide benefit by reducing plaque burden.

The toxicokinetic profile of aducanumab was evaluated in Tg2576 mice in 13-week and 6-month studies and in cynomolgus monkeys in a 4-week study. Of the 2 species, the Tg2576 mouse is considered the primary pharmacologically relevant species given that these mice accumulate amyloid plaques in the cerebral parenchyma and vasculature. In addition to the standard histopathological evaluation in mice, Perls' staining of hemosiderin (a breakdown product of hemoglobin) was performed to quantify microhemorrhage. Microhemorrhage has been observed both as a background finding in transgenic mouse models of AD [Winkler 2001], including Tg2576 mice [Kumar-Singh 2005], and as a drug-related finding in transgenic mice treated with some anti-Aβ antibodies [Pfeifer 2002; Racke 2005; Wilcock and Colton 2009].

Findings consistent with amyloid plaques and vascular amyloid were identified in the brain sections of animals in all groups, including the control group, as expected with this model. In both studies, repeated administration of ch12F6A or aducanumab was well tolerated with no treatment-related deaths observed during the dosing period. In the 13-week toxicology study, meningeal/cerebral vascular inflammation and/or vascular thickening were observed in mice dosed with ch12F6A $\geq$ 70 mg/kg compared with the control group. In the 6-month study, although slight differences were observed between ch12F6A-treated groups and the control group, animals treated with aducanumab were comparable to the control animals. The evaluation of microhemorrhage, characterized by quantification of hemosiderin in Perls stained brain sections of each main study and recovery animal, demonstrated no significant increase in scores with ch12F6A or aducanumab treatment in either study. The incidence and severity of hemorrhage or cerebral vascular inflammation were comparable in the 13-week and 6-month mouse studies.

See the Investigator's Brochure (IB) for detailed information on nonclinical studies.

5.1.2. Clinical Experience

Aducanumab has been evaluated in one completed single ascending dose study (221AD101) and one ongoing multiple ascending dose study (221AD103):

- Study 221AD101 was a Phase 1, randomized, double-blind, placebo-controlled, study of aducanumab in subjects with mild or moderate AD.

  The primary objective was to evaluate the safety and tolerability of a range of aducanumab doses (0.3 to 60 mg/kg) when administered as single intravenous (IV) infusions. The secondary objectives were to assess the pharmacokinetic (PK) and immunogenicity of aducanumab after single-dose administration.

  A single dose of aducanumab up to 30 mg/kg was demonstrated to be well tolerated. Dose-limiting ARIA (2 subjects with ARIA-E [edema] and 1 subject with ARIA-E and ARIA-H [microhemorrhage]) was observed in the 60 mg/kg dose group resulting in termination of further dosing in that cohort; no cases of ARIA were observed at single doses below 60 mg/kg. The PK profile was dose linear.

- Study 221AD103 is an ongoing randomized, double-blind, placebo-controlled multiple dose study of aducanumab in subjects with prodromal or mild AD who are amyloid positive. The study comprises a placebo-controlled period with subjects receiving monthly doses of aducanumab (fixed doses of 1, 3, 6, or 10 mg/kg, or titration up to 10 mg/kg) or placebo for a year followed by a dose-blind long-term extension (LTE) period with subjects receiving monthly doses of aducanumab. Note: The fixed-dose cohorts enrolled both apolipoprotein E4 (ApoE ε4) carriers and non-carriers while the titration cohort is comprised of ApoE ε4 carriers only.

  The primary objective of Study 221AD103 is to evaluate the safety and tolerability of multiple doses of aducanumab administered monthly as single IV infusions. The secondary objectives are to assess the effect of aducanumab on cerebral amyloid plaque content as measured by ^{18}F-florbetapir positron emission tomography (PET), and to evaluate the PK and immunogenicity of aducanumab after multiple-dose administration. Exploratory objectives include assessment of the effect of aducanumab on the clinical progression of AD as measured by CDR-sum of boxes (SB) and MMSE.

  In the most recent interim analysis (25 May 2017), the incidence of ARIA has been observed to be both dose- and ApoE ε4 carriage-dependent, especially at the highest doses when administered as a fixed dose. ARIA-E was radiographically monitored by magnetic resonance imaging (MRI) and typically observed early in treatment (between 2 to 5 doses). In most cases, ARIA-E resolved 4 to 12 weeks after onset and ARIA-H was typically stable 2 to 4 weeks after onset. In the placebo-controlled period, the incidence of ARIA-E appeared to be lower in the group receiving titration to 10 mg/kg (comprising ApoE ε4 carriers only; 8/23 [35%]) than in carriers in the 6 mg/kg and 10 mg/kg fixed-dose groups (9/21 [43%] and 11/20 [55%], respectively). Of note, among the subjects receiving titration to 10 mg/kg who had ARIA-E, the abnormalities were observed at the 3 and 6 mg/kg dose levels, before they reached

10 mg/kg. Also, 13 (of 23, 57%) subjects in the titration arm have been titrated to 10 mg/kg, and of these, 12 continued treatment and received at least 17 doses of 10 mg/kg; none of these subjects experienced ARIA-E or ARIA-H. Furthermore, ARIA-E events when they occurred (in the titration group) have been either asymptomatic or associated with mild symptoms that resolved, and most subjects who had ARIA-E continued treatment (6/8; 75%) compared with only 36% (4/11) of carriers in the fixed-dose 10 mg/kg arm (refer to the IB for details on events of ARIA). In the LTE period, the incidence of ARIA-E in ApoE ε4 carriers who were titrated up to 6 mg/kg (2 doses of 3 mg/kg, then 6 mg/kg) was 23% (3/13), with an overall rate of 16% (3/19) as no ApoE ε4 non-carriers (0/6) experienced ARIA-E.

Protocol-specified interim analyses of the ongoing multiple-ascending dose Study 221AD103 have demonstrated engagement of aducanumab with amyloid plaques, a pharmacodynamic (PD) effect on amyloid reduction, and an effect on CDR-SB and MMSE suggestive of a slowing of clinical decline in aducanumab-treated subjects. The dose- and time-dependent reduction of brain Aβ burden observed with aducanumab treatment was statistically significant at doses of 3, 6, and 10 mg/kg after 6 and 12 months of dosing, as well as with 1 mg/kg and titration from 1 to 10 mg/kg after 12 months of dosing. Further dose-dependent reductions in brain Aβ were observed for up to 36 months. Subjects who switched from placebo to aducanumab in the LTE period saw a reduction in brain Aβ similar to that seen by subjects who received aducanumab in the placebo-controlled period. The results demonstrate target engagement (amyloid plaques) and a PD effect (dose-dependent amyloid reduction).

In addition, results from the interim analyses showed an effect at 1 year on the exploratory endpoints CDR-SB and MMSE (at fixed doses of 1 mg/kg, 3 mg/kg, 6 mg/kg and 10 mg/kg compared with placebo), suggesting a reduction in the progression of clinical impairment for aducanumab-treated versus placebo-treated subjects. Furthermore, generally consistent treatment differences were seen for the fixed-dose cohorts, and in the titration group, effects on the CDR-SB and MMSE after 1 year were generally consistent with the fixed-dose results. Compared with placebo, adjusted mean changes from baseline to Week 54 in CDR-SB scores favored all aducanumab dose regimens tested, with treatment differences of 0.5 points or greater favoring aducanumab at doses of 3, 6, and 10 mg/kg and titration to 10 mg/kg, and statistical significance seen in the 10 mg/kg and titration groups. On the MMSE, adjusted mean decreases from baseline to Week 52 suggested a clinically meaningful benefit in the 3 and 10 mg/kg groups and the titration group and were significantly lower than placebo in the 10 mg/kg group. Furthermore, CDR-SB and MMSE data suggested a clinical benefit in those continuing on aducanumab up to 3 years compared with those who switched from placebo to aducanumab in the LTE period. Refer to the IB for details on interim analyses results.

5.2. Study Rationale

The purpose of this study is to assess the efficacy and safety of aducanumab compared with placebo in subjects with early AD including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD. Aducanumab is a human IgG1 monoclonal antibody that recognizes aggregated forms of Aβ, including soluble Aβ oligomers and deposited fibrillar Aβ. Earlier publications have demonstrated that both soluble oligomers and amyloid plaques are neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008] and clearance of amyloid plaques could lead to normalization of calcium homeostasis and neuronal activity, as well as reduction of oxidative stress in the brain of an animal model of AD [Rozkalne 2009; Spires-Jones 2009]. For this reason, treatment with aducanumab is expected to slow progression of AD, while preserving global function longer, when compared with untreated subjects.

Interim analyses of the ongoing multiple dose study (Study 221AD103) have demonstrated target engagement, a PD effect on amyloid reduction, and an effect on CDR-SB and MMSE suggestive of a reduction in the progression of clinical impairment for aducanumab-treated subjects. These results, along with the observed safety and tolerability profile, warrant the further Phase 3 investigation of aducanumab in a patient population spanning the early stages of the AD continuum.

5.3. Rationale for Dose and Schedule Selection

The dosing regimen selected for this study was based on the PK and PD relationship for removal of brain amyloid and effect on CDR-SB and MMSE observed in Study 221AD103 interim analyses and on safety, tolerability, and PK data from studies 221AD101 (complete) and 221AD103 (ongoing).

The dose- and time-dependent reduction of brain amyloid burden observed with aducanumab treatment in Study 221AD103 was statistically significant at doses of 3, 6, and 10 mg/kg after 6 months of dosing, and at 3, 6, and 10 mg/kg as well as with titration to 10 mg/kg after 12 months of dosing. On the exploratory endpoints of CDR-SB and MMSE changes from baseline, a dose-dependent slowing of clinical decline was observed for aducanumab versus placebo after 1 year of treatment. Compared with placebo, adjusted mean changes from baseline to Week 54 for CDR-SB favored all the aducanumab dose groups tested, with treatment differences of 0.5 points or greater at fixed doses of aducanumab 3, 6, and 10 mg/kg and also with titration to 10 mg/kg. On the MMSE, adjusted mean decreases from baseline to Week 52 were smaller in all dose groups than in the placebo group. Of note, on the CDR-SB, the point estimate for the titration group (comprising ApoE ε4 carriers only) was generally similar to that for the 10 mg/kg group and significantly lower than placebo in both those groups; on the MMSE, the point estimate for the titration group is generally similar to that in the 10 mg/kg group (which showed significantly less decline than placebo) and the 3 mg/kg group.

In the most recent interim analysis (25 May 2017), the incidence of ARIA has been observed to be both dose- and ApoE ε4 carriage-dependent, especially at the highest doses when administered as a fixed dose. However, the incidence of ARIA-E, as well as discontinuations from treatment due to ARIA-E, in subjects receiving aducanumab titrated to 10 mg/kg (ApoE ε4 carriers only) appear to be reduced (8/23 [35%]) compared with fixed doses of aducanumab at

6 mg/kg (9/21 [43%]) and 10 mg/kg (11/20 [55%]). Furthermore, among those subjects randomized to receive aducanumab titrated to 10 mg/kg, ARIA-E occurred only at the 3 mg/kg and 6 mg/kg dose levels. Also, 13 (of 23, 57%) subjects in the titration arm have been titrated to 10 mg/kg, and of these, 12 continued treatment and received at least 17 doses of 10 mg/kg; none of these subjects experienced ARIA-E or ARIA-H.

In an effort to maximize the dose-dependent amyloid reduction and effect on CDR-SB and MMSE that have been observed with doses of 3 mg/kg and higher while maintaining ARIA incidence, severity, and related discontinuation rate within acceptable levels, a titration regimen will be explored in this study. It has been suggested that the ARIA observed following treatment with amyloid targeting agents may be due, in part, to the initial large removal of amyloid and subsequent saturation of perivascular brain amyloid clearance mechanisms [Weller 2008]. Titration to the target dose is expected to result in slower initial amyloid removal, yet trigger alternative mechanisms of amyloid clearance including monoclonal antibody-dependent Fc-mediated microglial clearance [Ostrowitzki 2012], which would prevent saturation of amyloid clearance and subsequent ARIA during titration and once the target dose is reached. Since aducanumab-induced ARIA has been demonstrated to occur early during treatment, with most cases occurring within the first 5 doses, titration of aducanumab for up to 6 doses prior to reaching the target dose may result in reduction of ARIA incidence and severity.

Given the tolerability and apparent efficacy of aducanumab shown, the doses to be tested using a titration regimen are 3 and 10 mg/kg for ApoE ε4 carriers, and 6 and 10 mg/kg for ApoE ε4 non-carriers. Titration will start at 1 mg/kg and will escalate to 3, 6, and 10 mg/kg as detailed below.

5.3.1. Dosing Scheme

5.3.1.1. Placebo-Controlled Period

Doses will be administered approximately 4 weeks apart, over approximately 76 weeks (a total of 20 doses). Based upon their ApoE ε4 carrier status, subjects will be assigned to 1 of 3 treatment groups (approximately 535 subjects each [see Section 16.8]) in a 1:1:1 ratio (aducanumab low dose:aducanumab high dose:placebo) as follows (Table 12 and Figure 1):

ApoE ε4 Carrier

- Low dose (3 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg thereafter

- High dose (10 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter

- Placebo

  Saline infusion

ApoE ε4 Non-Carrier

- Low dose (6 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 4 doses, and 6 mg/kg thereafter

- High dose (10 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter

- Placebo

  Saline infusion

Table 12: Dosing Scheme for Aducanumab by Treatment Group and ApoE ε4 Carrier Status

Dose (Month)		1	2	3	4	5	6	7 to 20
Treatment Group		Dose (mg/kg)						
ApoE ε4 (+)	Low Dose	1	1	3	3	3	3	3
	High Dose	1	1	3	3	6	6	10[1]
	Placebo	saline						
ApoE ε4 (-)	Low Dose	1	1	3	3	3	3	6
	High Dose	1	1	3	3	6	6	10
	Placebo	saline						

[1] 10 mg/kg is the target dose for all ApoE ε4 carriers assigned to the aducanumab high-dose group. Subjects enrolled under protocol versions prior to Version 4 and assigned to the previous high-dose of 6 mg/kg will be titrated to 10 mg/kg upon receipt of at least 2 doses at 6 mg/kg.

5.3.2. Dosing Scheme Modification

An independent data monitoring committee (IDMC) will review unblinded safety data, including serious AEs (SAEs) and incident cases of ARIA, from all ongoing aducanumab studies (e.g., Studies 221AD103, 221AD104, 221AD301, and 221AD302) as described in the IDMC charter.

The dosing scheme can be modified in the following circumstances:

- Safety and tolerability of the high dose

  If the high dose (10 mg/kg) is deemed not acceptable, enrollment for the high-dose group(s) will be terminated and subjects will not be replaced. Subjects who have already been randomized to the discontinued dose will be down-dosed to the next available dose according to their ApoE ε4 carrier status. Definition of low and high-dose groups will be revised as described in Section 16.

5.3.3. Long-Term Extension Period

Subjects who received aducanumab in the placebo-controlled period and who enter the LTE period will maintain the dosing scheme outlined in the protocol at the time of transition from the placebo-controlled period to the LTE period (e.g., subjects who are on stable dosing in the placebo-controlled period will continue on the same dose, subjects who are on a titration regimen during the transition will continue to titrate into the LTE period and subjects who complete the placebo-controlled period under protocol versions prior to Version 4 and are assigned to the high dose aducanumab treatment group may up titrate to 10 mg/kg in the LTE). Subjects randomized to placebo at the start of the placebo-controlled period (Study Day 1) will also be randomized to receive dose-blinded aducanumab (low dose:high dose, 1:1 ratio) for the LTE period. Randomization will be stratified by subject ApoE ε4 carrier status. Subjects will be dosed using the same regimen described for the placebo-controlled period (see Table 12 and Figure 1).

Any modifications to the dosing scheme (i.e., termination of high-dose group, as described in Section 5.3.2) will also be implemented in the LTE period.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

The primary objective of the study is to evaluate the efficacy of monthly doses of aducanumab in slowing cognitive and functional impairment as measured by changes in the CDR-SB score as compared with placebo in subjects with early AD.

The primary endpoint that relates to this objective is change from baseline in CDR-SB score at Week 78.

6.2. Secondary Objectives and Endpoints

A secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by the MMSE.

- The endpoint that relates to this objective is change from baseline in MMSE score at Week 78.

Another secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by ADAS-Cog 13.

- The endpoint that relates to this objective is change from baseline in ADAS-Cog 13 score at Week 78.

Another secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by ADCS-ADL-MCI.

- The endpoint that relates to this objective is change from baseline in ADCS-ADL-MCI score at Week 78.

6.3. Tertiary Objectives and Endpoints

6.3.1. Tertiary Objectives

Safety and Tolerability

- To assess the safety and tolerability of monthly doses of aducanumab.
- To assess the immunogenicity of aducanumab.

Biomarker/Efficacy/Health Outcomes

- To assess the effect of aducanumab on cerebral amyloid plaque content as measured by amyloid PET imaging (in a subset of approximately 400 subjects).
- To assess the effect of aducanumab on behavior as measured by the Neuropsychiatric Inventory-10 (NPI-10).
- To assess the effect of aducanumab on subject health status, measured by EuroQol health status measures (EQ-5D [informant-rated and subject self-reported]).

- To assess the effect of aducanumab on subject self-reported cognitive function, measured by the modified Perceived Deficits Questionnaire-20 (mPDQ-20) [Lenderking 2014].
- To assess the correlation between primary endpoint and cerebral amyloid plaque content as measured by PET imaging.

Pharmacokinetics

- To collect and characterize the PK parameters of aducanumab in serum.

6.3.2. Tertiary Endpoints

Safety and Tolerability

- Incidence of all AEs and SAEs.
- Brain MRI findings including incidence of ARIA-E and ARIA-H.
- Clinical laboratory shifts in reported values.
- Clinically significant changes in vital sign measurements and electrocardiograms (ECGs).
- Incidence of anti-aducanumab antibodies in serum.

Biomarkers/Efficacy/Health Outcomes

- Change from baseline in amyloid PET signal at Week 26 (in a subset of sites and subjects).
- Change from baseline in amyloid PET signal at Week 78 (in a subset of sites and subjects).
- Change from baseline in NPI-10 score at Week 78.
- Change from baseline in subject self-reported EQ-5D index score at Week 78.
- Change from baseline in informant-rated subject EQ-5D index score at Week 78.
- Change from baseline in mPDQ-20 at Week 78.
- Correlation between the primary endpoint and cerebral amyloid plaque content as measured by PET imaging over time.

Pharmacokinetics

- Serum concentrations and PK parameters of aducanumab.

6.4. Additional Exploratory Objectives and Endpoints

6.4.1. Additional Exploratory Objectives

Biomarkers

- To assess the effect of aducanumab on various morphometric measures in certain brain areas as measured by MRI.
- To assess the effect of aducanumab on functional connectivity by task-free functional MRI (tf-fMRI) [where available, in a subset of sites and subjects].
- To assess the effect of aducanumab on cerebral blood flow by arterial spin labeling (ASL)-MRI (where available, in a subset of sites and subjects).
- To assess the effect of aducanumab on disease- or treatment-related biomarkers in CSF, which may include, but are not limited to, amyloid and tau proteins (in a subset of subjects).
- To assess the effect of aducanumab on disease- or treatment-related biomarkers in blood, which may include, but are not limited to, amyloid and tau proteins.
- To assess the effect of aducanumab on tau pathology by tau PET imaging (where available, in a subset of sites and subjects).

Health Outcomes

- To assess the effect of aducanumab on the informant/care partner's own health status, measured by the EQ-5D.
- To assess the effect of aducanumab on caregiver burden as measured by the Caregiver Assessment Measure (CAM).

6.4.2. Additional Exploratory Endpoints

Biomarkers

- Change from baseline in whole brain volume, hippocampal volume, ventricular volume, and cortical gray matter volume measured by MRI over time.
- Change from baseline in functional connectivity as measured by tf-fMRI over time (where available, in a subset of sites and subjects).
- Change from baseline in cerebral blood flow as measured by ASL-MRI over time (where available, in a subset of sites and subjects).
- Change from baseline in CSF biomarkers, which may include, but are not limited to, amyloid or tau proteins at Week 78 (in a subset of subjects).
- Change from baseline over time in blood biomarkers, which may include, but are not limited to, amyloid or tau proteins.
- Change from baseline in tau PET signal at Week 78 (where available, in a subset of sites and subjects).

Health Outcomes

- Change from baseline in informant/care partner's own EQ-5D index-score at Week 78.

- Changes on the CAM over time.

6.5. Long-Term Extension Objectives and Endpoints

6.5.1. Tertiary LTE Objectives

- To evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD.
- To evaluate the long-term efficacy of aducanumab treatment as measured by clinical, radiological, and health outcomes assessments.

6.5.2. Tertiary LTE Endpoints

- The incidence of AEs and/SAEs; brain MRI findings (including the incidence of ARIA-E and ARIA-H); and the incidence of anti-aducanumab antibodies in serum over the placebo-controlled and LTE periods of the study.
- Change in the following measures over the placebo-controlled and LTE periods of the study:
  - CDR-SB score.
  - MMSE score.
  - ADAS-Cog 13 score.
  - ADCS-ADL-MCI score.
  - Amyloid PET signal (in a subset of sites and subjects).
  - NPI-10 total score.
  - Informant-rated EQ-5D index score.

6.5.3. Additional Exploratory LTE Objective

- To evaluate the long-term efficacy of aducanumab treatment as measured by radiological, clinical, and additional health outcomes.

6.5.4. Additional Exploratory LTE Endpoints

- Change in the following measures over the placebo-controlled and LTE periods of the study:
  - Whole brain volume, hippocampal volume, ventricular volume, and cortical gray matter volume measured by MRI.
  - Functional connectivity as measured by tf-fMRI (where available, in a subset of sites and subjects).
  - Cerebral blood flow as measured by ASL-MRI (where available, in a subset of sites and subjects).

- Disease- or treatment-related biomarkers levels in CSF, which may include, but are not limited to, amyloid and tau proteins (in a subset of subjects).
- Disease- or treatment-related biomarker levels in blood, which may include, but are not limited to, amyloid and tau proteins.
- Informant/care partner's own self-reported EQ-5D index score.
- CAM.
- Tau PET signal (where available, in a subset of sites and subjects).

7. STUDY DESIGN

7.1. Study Overview

Study 221AD301 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 study in subjects with early AD, including MCI due to AD and a subset of mild AD, followed by an optional dose-blinded LTE period of up to 5 years. Approximately 1605 subjects (see Section 16.8) will be enrolled across approximately 150 centers globally. The primary study objective is to evaluate the efficacy of monthly doses of aducanumab on the CDR-SB relative to placebo. Secondary objectives include assessment of the effect of monthly doses of aducanumab on clinical progression as compared to placebo. The safety of monthly doses of aducanumab will also be evaluated.

Subjects will receive infusions of aducanumab or placebo approximately every 4 weeks for approximately 18 months (a total of 20 doses). Subjects will be randomized to receive aducanumab low dose:aducanumab high dose:placebo in a 1:1:1 ratio. The randomization will be stratified by site and ApoE ε4 status (carrier or non-carrier). The ratio of ApoE ε4 carriers to non-carriers in the study population will generally reflect the distribution in the broader AD population. Enrollment will also be monitored, via interactive response technology (IRT), such that subjects with mild AD represent a small percentage of the total enrolled in the trial.

At the end of the double-blind, placebo-controlled treatment period, subjects who meet the extension entry criteria may enter a long-term safety and efficacy extension period, with all subjects receiving aducanumab approximately every 4 weeks (up to a total of 65 doses over 5 years). The EOT Visit will occur at Week 338, or when the last subject has had his or her Week 182 Visit, whichever occurs first.

The total duration of study participation for each subject only participating in the placebo-controlled period of the study will be up to approximately 102 weeks, including a series of screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, and a safety follow-up (FU) period of 18 weeks after the final dose.

The total duration of study participation for each subject participating in the placebo-controlled period and the LTE period will vary and be up to approximately 362 weeks, including a series of screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, a 4-week FU period, a 256-week aducanumab dose-blind treatment period, and a safety FU period of 18 weeks after the final dose. The FU period of 18 weeks is based on an estimated mean elimination half-life in humans of 16 to 24 days (mean approximately 20 days, based on results from the single ascending dose study [Study 221AD101]) and anticipated brain concentrations of aducanumab of less than one-third the EC_{50} (inhibitory concentration at 50% of the maximum observed biologic effect) for binding fibrillar amyloid at 8 weeks after the last dose.

During the placebo-controlled period, ApoE ε4 carriers will receive placebo, aducanumab 3 mg/kg, or aducanumab 10 mg/kg whereas ApoE ε4 non-carriers will receive

placebo, aducanumab 6 mg/kg, or aducanumab 10 mg/kg. Aducanumab will be titrated for up to 6 doses prior to reaching the target dose as shown in Table 12 and Figure 1. Note: As of Protocol Version 4, 10 mg/kg is the target dose for all ApoE ε4 carriers in the high-dose group. ApoE ε4 carriers who were randomly assigned to the high-dose group when the target dose was 6 mg/kg (under protocol versions prior to Version 4) must have received 2 or more doses at 6 mg/kg prior to being titrated up to 10 mg/kg. Subjects who received placebo during the placebo-controlled period will be assigned to treatment based upon their ApoE ε4 carrier status in a 1:1 ratio (aducanumab low dose:aducanumab high dose) for the LTE period, and aducanumab will be titrated for up to 6 doses prior to reaching the target dose following the same schedule described for the placebo-controlled period.

See Section 5.3.2 for details of dosing scheme modification.

Individual dose adjustments may also be implemented in subjects who develop ARIA. See Section 7.2.1.

Investigators, study site staff (except for the designated unblinded pharmacist/technician), and study subjects will be blinded to the subjects' randomized treatment assignment for the placebo-controlled period. During the LTE period, Investigators and subjects will remain blinded to the treatment assignment in the placebo-controlled period and the aducanumab dose for the LTE period.

7.2. Study Specifics

7.2.1. Dose Suspension, Modification, or Termination for ARIA Events

Discontinuation of Dosing for a Given Subject

The central MRI reading center will report incident cases of ARIA-E and ARIA-H to both the Sponsor and the PI within a specified time after observing the finding on MRI per the imaging manual procedures. All cases of ARIA will be reviewed by the Sponsor and the PI; decisions on dosing continuation, interruption, or discontinuation will be based on clinical symptoms, and the MRI information provided by the central reader. IDMC notification rules will be outlined in the IDMC charter. Guidelines on the management and disposition of ARIA-E and ARIA-H cases (including the criteria to be met for the continuation, suspension/resumption, permanent discontinuation of dosing due to ARIA, resumption of dosing after dose suspension due to ARIA [including rules for titrating up to the assigned dose], and management of recurrent ARIA) are provided in the following subsections. Dosing may also be terminated at the discretion of the Sponsor for medical reasons. See Section 10.1 for the full list of criteria for discontinuing study treatment.

7.2.1.1. ARIA-E Cases

Table 13: Disposition of ARIA-E Cases

<table>
<tr><th rowspan="2">Clinical Symptom Severity</th><th colspan="3">ARIA-E Severity on MRI (Central Read)</th></tr>
<tr><th>Mild</th><th>Moderate</th><th>Severe</th></tr>
<tr><td>Asymptomatic</td><td>Continue dosing at current dose and schedule</td><td colspan="2">Suspend dosing. Once ARIA-E resolves the subject may resume dosing at the same dose.</td></tr>
<tr><td>Mild</td><td colspan="3" rowspan="4">Suspend dosing. Once ARIA-E and clinical symptoms resolve, the subject may resume dosing at the same dose.</td></tr>
<tr><td>Moderate</td></tr>
<tr><td>Severe</td></tr>
<tr><td>Serious "other medically important event" only[1]</td></tr>
<tr><td>Serious, except for "other medically important event"[2]</td><td colspan="3">Discontinue Dosing</td></tr>
</table>

[1] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above and as described in Section 15.1.2.

[2] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.1.2.

- Subjects who develop **mild ARIA-E, per central MRI reading, with no clinical symptoms** at any time during the study may continue in the study at their current dose. Subjects should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-E has resolved per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. The Sponsor may require that the subjects discontinue dosing or continue dosing at a lower dose level based on review of safety and MRI data.
- Subjects who develop **moderate or severe ARIA-E, per central MRI reading, with no clinical symptoms** at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-E has resolved per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. If the ARIA-E has resolved and the subjects remain asymptomatic (in the Investigator's opinion), the subjects may resume treatment at the same dose.

- Subjects who develop **mild, moderate, or severe ARIA-E, per central MRI reading, accompanied by mild, moderate, severe, or serious ("other medically important event" only) clinical symptoms** at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-E has resolved per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. If the ARIA-E has resolved and the clinical symptoms have resolved (in the Investigator's opinion), the subject may resume treatment at the same dose.
- Subjects who develop mild, moderate, or severe ARIA-E, per central MRI reading, accompanied by serious (except "other medically important event") clinical symptoms at any time during the study will permanently discontinue treatment but remain in study. Subjects should complete a FU Visit 18 weeks after the final dose, protocol-required tests and assessments at a subset of the clinic visits (see Table 10, and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-E has resolved per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.

See Section 7.2.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.1.2. ARIA-H (Microhemorrhage)

In this study, new incident microhemorrhages are defined as new incident microhemorrhages that occur on treatment and do not include microhemorrhages at baseline.

Table 14: Disposition of ARIA-H (Microhemorrhage) Cases

<table>
<tr><th rowspan="2">Clinical Symptom Severity</th><th colspan="3">New Incident Microhemorrhages[1] (Central Read)</th></tr>
<tr><th>Mild</th><th>Moderate</th><th>Severe</th></tr>
<tr><th></th><th>≥ 1 and ≤ 4</th><th>≥ 5 and ≤ 9</th><th>≥ 10</th></tr>
<tr><td>Asymptomatic</td><td>Continue dosing at current dose and schedule</td><td>Suspend dosing. Once ARIA-H is stable, the subject may resume dosing at the same dose.</td><td rowspan="5">Discontinue dosing</td></tr>
<tr><td>Mild</td><td colspan="2" rowspan="4">Suspend dosing. Once ARIA-H stabilizes and clinical symptoms resolve, the subject may resume dosing at the same dose.</td></tr>
<tr><td>Moderate</td></tr>
<tr><td>Severe</td></tr>
<tr><td>Serious "other medically important event" only[2]</td></tr>
<tr><td>Serious, except for "other medically important event"[3]</td><td colspan="2">Discontinue dosing</td></tr>
</table>

[1] New incident microhemorrhages = new incident microhemorrhages on treatment; does not include microhemorrhages at baseline.

[2] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above as described in Section 15.1.2.

[3] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.1.2.

Asymptomatic ARIA-H (Microhemorrhage)

- Subjects who develop a **≥ 1 and ≤ 4 new incident microhemorrhage(s) [mild]** at any time during the study may continue treatment at the current dose.
- Subjects who develop **≥ 5 and ≤ 9 new incident microhemorrhages [moderate]** occurring at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the microhemorrhage is confirmed as stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. A microhemorrhage is considered stable if there is no change or a decrease in the number, size, severity, or number of locations between 2 consecutive MRIs including the initial detection MRI and the MRI performed 4 weeks (±5 days) later. Once the microhemorrhage is deemed stable, subjects may resume treatment at the same dose.

- Subjects who develop **≥ 10 new incident microhemorrhages [severe]** during the study will permanently discontinue treatment but remain in study. Subjects should complete a FU Visit 18 weeks after the final dose, protocol-required tests and assessments at a subset of the clinic visits (see Table 10 and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the microhemorrhages are deemed stable per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.

Symptomatic ARIA-H (Microhemorrhage)

- Subjects who develop **≤ 9 new incident microhemorrhages (mild or moderate) and mild, moderate, severe, or serious ("other medically important event" only [Section 15.1.2]) clinical symptoms** will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-H (microhemorrhage(s) is confirmed stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. Microhemorrhages are considered stable if there is no change or a decrease in the number, size, severity, or number of locations between 2 consecutive MRIs including the initial detection MRI and the MRI performed 4 weeks (±5 days) later. Once ARIA-H (microhemorrhage) is deemed stable and the clinical symptoms have resolved (in the Investigator's opinion), the subject may resume treatment at the same dose.
- Subjects who experience **serious (except "other medically important event" [Section 15.1.2]) clinical symptoms associated with microhemorrhage(s)** will permanently discontinue treatment but remain in study. Subjects should complete a FU Visit 18 weeks after the final dose, protocol-required tests and assessments at a subset of the clinic visits (see Table 10 and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the microhemorrhage(s) is confirmed stable per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.
- Subjects who develop **≥ 10 new incident microhemorrhages (severe)**, regardless of symptom severity, during the study will permanently discontinue treatment but remain in study. Subjects should complete a FU Visit 18 weeks after the final dose, protocol-required tests and assessments at a subset of the clinic visits (see Table 10 and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the microhemorrhages are deemed stable per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.

See Section 7.2.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.1.3. ARIA-H (Superficial Siderosis)

Table 15: Disposition of ARIA-H (Superficial Siderosis) Cases

<table>
<tr><td rowspan="2">Clinical Symptom Severity</td><td colspan="3">New Incident Areas of Superficial Siderosis[1] (Central Read)</td></tr>
<tr><td>Mild</td><td>Moderate</td><td>Severe</td></tr>
<tr><td></td><td>1</td><td>2</td><td>>2</td></tr>
<tr><td>Asymptomatic</td><td>Continue dosing at current dose and schedule</td><td>Suspend dosing. Once ARIA-H is stable the subject may resume dosing at the same dose.</td><td rowspan="5">Discontinue dosing</td></tr>
<tr><td>Mild</td><td colspan="2" rowspan="4">Suspend dosing. Once ARIA-H stabilizes and clinical symptoms resolve, the subject may resume dosing at the same dose.</td></tr>
<tr><td>Moderate</td></tr>
<tr><td>Severe</td></tr>
<tr><td>Serious "other medically important event" only[2]</td></tr>
<tr><td>Serious, except for "other medically important event"[3]</td><td colspan="2">Discontinue dosing</td></tr>
</table>

[1] New incident superficial siderosis = new incident superficial siderosis on treatment.

[2] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above as described in Section 15.1.2.

[3] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.1.2.

Asymptomatic ARIA-H (Superficial Siderosis)

- Subjects who develop a **single incident focal area of hemosiderosis (also referred to as superficial siderosis) [mild]** may continue treatment at the current dose, but must have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the superficial siderosis is confirmed as stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. Superficial siderosis is considered stable if there is no change or a decrease in the number, size, severity, or number of locations between 2 consecutive MRIs, including the initial detection MRI and the MRI performed 4 weeks (±5 days) later.
- Subjects who develop **2 focal areas of hemosiderosis (superficial siderosis) [moderate]** occurring at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in

addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-H (superficial siderosis) is confirmed as stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. Once the superficial siderosis is deemed stable, the subjects may resume treatment at the same dose.

- Subjects who develop >**2 focal areas of hemosiderosis (superficial siderosis) [severe]** occurring at any time during the study must permanently discontinue treatment but remain in study. Subjects should complete a FU Visit 18 weeks after the final dose, protocol-required tests and assessments at a subset of the clinic visits (see Table 10 and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-H (superficial siderosis) is confirmed as stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.

Symptomatic ARIA-H (superficial siderosis)

- Subjects who develop **≤ 2 new focal areas of superficial siderosis (mild or moderate)** and **mild, moderate, severe, or serious ("other medically important event" only)** clinical symptoms will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-H superficial siderosis is confirmed stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. Superficial siderosis is considered stable if there is no change or a decrease in the number, size, severity, or number of locations between 2 consecutive MRIs including the initial detection MRI and the MRI performed 4 weeks (±5 days) later. Once the ARIA-H (superficial siderosis) is deemed stable and the clinical symptoms have resolved (in the Investigator's opinion), the subjects may resume treatment at the same dose.
- Subjects who experience **serious (except "other medically important event" [Section 15.1.2]) clinical symptoms associated with ARIA-H (superficial siderosis)** will permanently discontinue treatment but remain in study. Subjects should complete a FU Visit 18 weeks after the final dose, protocol-required tests and assessments at a subset of the clinic visits (see Table 10 and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the superficial siderosis is confirmed stable per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.
- Subjects who develop **>2 new focal areas of superficial siderosis (severe)** regardless of clinical symptom severity will permanently discontinue treatment but remain in study. Subjects should complete a FU Visit 18 weeks after the final dose, protocol-required tests and assessments at a subset of the clinic visits (see Table 10 and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA

every 4 weeks (±5 days) until the superficial siderosis is confirmed stable per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.

See Section 7.2.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.1.4. ARIA-H (Macrohemorrhage)

Subjects who develop any new incident macrohemorrhage (defined as >1 cm in diameter on T2* sequence), regardless of symptom severity during the study, will permanently discontinue treatment, but remain in study. Subjects should complete a FU Visit 18 weeks after the final dose, protocol-required tests and assessments at a subset of the clinic visits (see Table 10 and Table 11) and, in addition, have an unscheduled visit for MRI and MOCA every 4 weeks (±5 days) until the macrohemorrhage is confirmed stable per centrally read MRI. A macrohemorrhage is considered stable if there is no change or a decrease in the number, size, severity, or number of locations between 2 consecutive MRIs, including the initial detection MRI and the MRI performed 4 weeks (±5 days) later. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA-H (macrohemorrhage).

7.2.1.5. Coincident ARIA-H and ARIA-E Cases

Subjects who develop ARIA-H coincident with ARIA-E at any time during the study will follow the most restrictive guidelines. Prior to resuming treatment, where applicable, ARIA-E must resolve, ARIA-H must be deemed stable, and the subject must be asymptomatic. For example, if a subject experiences asymptomatic ARIA-H (1-4 microhemorrhages) coincident with ARIA-E assessed as moderate on MRI and accompanied by mild clinical symptoms, the dose should be suspended per the ARIA-E guidelines summarized in Table 13. In addition, unscheduled visits should occur as described in Section 7.2.1.1 through Section 7.2.1.4.

7.2.1.6. Resumption of Study Treatment After Suspension due to ARIA

7.2.1.6.1. MRI Monitoring

When treatment resumes after a dose suspension due to ARIA, an MRI and MOCA will be performed 2 weeks (±5 days) after the second administration of the restarted dose. In addition, if treatment was suspended during the dose titration prior to the subject reaching the maximum assigned dose, an MRI and MOCA will be performed 2 weeks (±5 days) after every second dose until completion of the titration period, with subjects assumed to be titrating to 10 mg/kg (titration period of 6 doses and a final MRI after the second dose at 10 mg/kg) to maintain study blinding, not counting unscheduled MRI visits for monitoring of ARIA. MRIs will otherwise be performed as indicated in the Schedule of Events (Section 4.2).

7.2.1.6.2. Dosing Upon Resumption of Study Treatment

Subjects who suspend treatment due to ARIA may resume treatment at the same dose if they meet the criteria as described in Sections 7.2.1.1 to 7.2.1.5. Subjects who suspend and then resume dosing after having already reached their assigned top dose level are to continue dosing at that dose level. However, if dosing is suspended prior to a subject reaching their assigned top dose level, the subject (1) must receive at least 2 doses at the restart dose before titrating up to the next dose level and (2) must complete at least the required number of doses at that dose level per their assigned treatment group, as outlined in the right column of Table 16.

Table 16: Resumption of Study Treatment Following Dose Suspension Due to ARIA During Titration

Assigned Treatment Group (Maximum Dose)	Dose Level at Which ARIA Occurred	Number of Doses Prior to ARIA	Number of Doses at Current Dose Level Needed Before Going to the Next Higher Dose
ApoE ε4 (+)			
Low Dose (3 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
High Dose (10 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	2
	3 mg/kg	2	2
	6 mg/kg	1	2
	6 mg/kg	2	2
ApoE ε4 (-)			
Low Dose (6 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	3
	3 mg/kg	2	2
	3 mg/kg	3	2
	3 mg/kg	4	2
High Dose (10 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	2
	3 mg/kg	2	2

Assigned Treatment Group (Maximum Dose)	Dose Level at Which ARIA Occurred	Number of Doses Prior to ARIA	Number of Doses at Current Dose Level Needed Before Going to the Next Higher Dose
	6 mg/kg	1	2
	6 mg/kg	2	2

7.2.1.7. Management After Recurrent ARIA (Dosing and MRI)

If the subject has more than one occurrence of ARIA (i.e., a second or any additional occurrences of ARIA-E or of ARIA-H, or ARIA-E and ARIA-H) that requires dose suspension (per criteria in Section 7.2.1.1, Section 7.2.1.2, and Section 7.2.1.3), after the ARIA resolves or stabilizes, the subject is to resume dosing at the same dose as that described in Section 7.2.1.6.2. Once dosing has resumed, the guidelines outlined in Table 16 apply. If a subject resumes treatment after ARIA, an MRI and MOCA will be performed 2 weeks (±5 days) after the second administration of the restarted dose, and 2 weeks (±5 days) after every second dose until the completion of titration, with all subjects assumed to be titrating to 10 mg/kg (6 doses) to maintain study blinding. MRIs will otherwise be performed as indicated in the Schedule of Events (Section 4.2).

Subjects who develop ARIA during the placebo-controlled period but continue or resume treatment at an active dose are eligible to enter the LTE period and will maintain the dosing scheme from the placebo-controlled period into the LTE, which may include a continuation on the same dose or completion of titration into the LTE period.

For subjects who discontinued treatment due to a third ARIA event that required dose suspension under a previous version of the protocol and remained on the study: these subjects will not resume dosing.

For subjects who resumed dosing at the next lower dose after recurrent ARIA under a previous version of the protocol and have not titrated to their target dose: these subjects will continue dosing (i.e., receive 2 doses at that dose level before titrating up to the next higher dose).

For subjects who dose-reduced to placebo after recurrent ARIA under a previous version of the protocol and remained in the study: these subjects can resume dosing during the LTE period and will be titrated up to his or her randomly assigned dose using the same regimen as that described for the placebo-controlled period (see Table 12 and Figure 1).

For subjects who dose-reduced to placebo after recurrent ARIA and then resumed dosing at aducanumab 1 mg/kg during the LTE period under a previous version of the protocol: these subjects can be titrated up to his or her randomly assigned dose using the same regimen as that described for the placebo-controlled period (see Table 12 and Figure 1).

For subjects who had dose suspension due to a recurrent ARIA event prior to the implementation of Protocol Version 6.0 that did not resolve or stabilize until after the implementation of Protocol Version 6.0: these subjects are to resume dosing at the same dose as that described in Section 7.2.1.6.2.

7.2.2. Infusion Interruption

If any mild or moderate infusion-related reactions (e.g., headache, chills/rigors, and nausea/vomiting) occur during an infusion, the infusion should be slowed or interrupted and supportive treatment should be instituted at the discretion of the Investigator. After resolution of symptoms, if the infusion had been slowed, the original infusion rate may be resumed; if the infusion had been interrupted, the infusion may be restarted at a rate that does not exceed the original infusion rate. An infusion must be discontinued if not completed within 3 hours.

Refer to the Directions for Handling and Administration (DHA) for infusion rate information.

If a severe infusion-related reaction occurs during an infusion, or an allergic reaction such as urticaria or anaphylaxis occurs, the subject will be discontinued from study treatment but may remain in the study. The subject must be appropriately treated in accordance with local practice.

Severity of events is described in Section 15.2.3.

7.3. Overall Study Duration and Follow-Up

The study period will consist of Screening, treatment, and FU.

The double-blind, placebo-controlled period of the study will consist of an 8-week screening period, a 76-week treatment period, and a safety FU period of 18 weeks after the final dose.

Subjects will have approximately 32 scheduled clinic visits during the placebo-controlled period, and up to 8 telephone safety FU contacts, as follows:

- Screening Visits no more than 60 days before the first dose of study treatment on Day 1 (visits will be conducted on multiple days). It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.
- 20 outpatient dosing visits.
- 8 telephone safety FU contacts approximately 2 weeks after each of the first 8 doses.
- 3 visits for clinical assessments.
- 2 visits (including baseline) for CSF biomarkers (optional). Note: CSF collection at Screening using study-specific procedures is preferred; however, if a CSF sample has been obtained within 3 months prior to Screening, this sample may be used in lieu of requiring that the subject undergo a lumbar puncture (LP) at Screening.
- 3 visits (including Screening) for amyloid PET scan (in a subset of subjects).
- 2 visits (including baseline) for tau PET scan (in a subset of subjects, where available).
- 7 visits for brain MRI.

- 1 FU safety visit at Week 94 (only for subjects not entering the LTE period) or 18 weeks after last administration of study treatment for those subjects who withdraw from study.

Subjects who meet the LTE inclusion and exclusion criteria will be eligible to enter the LTE period. Subjects who enter the LTE period will have approximately up to 76 additional planned clinic visits, and up to 8 telephone safety FU contacts, as follows:

- 65 outpatient dosing visits.
- 8 telephone safety FU contacts approximately 2 weeks after each of the first 8 doses.
- 7 visits for clinical assessments.
- 2 visits for CSF biomarkers (optional).
- 4 visits for amyloid PET scan (in a subset of subjects).
- 2 visits for tau PET scan (in a subset of subjects, where available).
- 10 visits for brain MRI.
- 1 FU safety visit.

Subjects who have a change in AD medication (other than study treatment) during the placebo-controlled or LTE period should have an unscheduled visit; all clinical assessments for the primary and secondary endpoints should be performed prior to the change in medication.

Subjects who experience ARIA during the placebo-controlled or LTE period should have unscheduled visits per the guidelines in Section 7.2.1.

7.3.1. Screening

During the Screening Visit, under a separate (optional) initial consent process, subjects can complete the neurocognitive scales (CDR, MMSE, the Repeatable Battery for Assessment of Neuropsychological Status [RBANS]) and ApoE genotyping. This initial neurocognitive screening is intended to reduce the burden on subjects and sites by avoiding unnecessary testing if subjects do not meet key inclusion criteria. If the subject meets inclusion criteria for these 3 scales, then the full consent process must be completed prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process, which would allow the administration of all screening assessments.

The neurocognitive assessments that have exclusion cut points (CDR, MMSE, and RBANS) and ApoE genotyping must be performed at Screening Visit 1. ApoE genotyping may be performed at Visit 1 prior to other screening assessments. The ADAS-Cog 13 and ADCS-ADL-MCI will be performed at Screening Visit 2 within 20 days after Visit 1 and must NOT be performed on the same day as the CDR, MMSE, and RBANS. The NPI-10 can be performed at any time during Screening as long as it is performed after the CDR (e.g., including at Screening Visit 1). All other cognitive assessments as well as CSF collection may be performed at any time during Screening after eligibility is confirmed during Screening Visit 1. CSF collection at Screening using study-specific procedures is preferred; however, if a CSF sample has been obtained within

3 months prior to Screening, this sample may be used in lieu of requiring an LP at Screening. The MRI at Screening Visit 2 should be done only after the subject eligibility based on clinical and laboratory criteria is confirmed during Screening Visit 1. The PET scan at Screening Visit 3 should be completed only after the MRI inclusion criterion is met.

Subject eligibility for the study will be determined no more than 60 days prior to study entry. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.

Subjects who fail Screening will be permitted to be rescreened once at the Sponsor's discretion. Subjects who fail Screening due to not meeting entry criteria for PET, MMSE, hepatitis B or C results, having a CDR global score >0.5, or having abnormal MRI findings will not be allowed to rescreen. Note: Subjects with a CDR global score of 0 but who meet the other entry criteria may repeat the screening CDR evaluation after 6 months of the initial evaluation.

Subjects who fail Screening because allowed chronic medications have not been at stable doses for at least 4 weeks prior to Screening Visit 1 or whose use of AD medications has not been at stable doses for at least 8 weeks prior to Screening Visit 1 may return for rescreening after use of these medications has been stabilized for the required period.

7.3.2. Treatment

Eligible subjects will report to the study site to receive study treatment every 4 weeks for 76 weeks (20 doses). All subjects who meet the LTE inclusion and exclusion criteria will be eligible to enter the LTE period and will receive study treatment every 4 weeks for up to an additional 256 weeks (65 doses), with the first dose administered approximately 4 weeks after the final dose in the placebo-controlled period of the study. Subjects will continue treatment once every 4 weeks, until Week 336, or until the last subject has had his or her Week 182 Visit, whichever occurs first.

7.3.3. Follow-Up

All subjects participating in the placebo-controlled period are to return to the study site approximately 2 weeks after the final dose for clinical assessments.

Subjects participating in the placebo-controlled period and not entering the LTE period are to return to the study site for a FU Visit at Week 94 (18 weeks after the last placebo-controlled period dose). The final study visit for these subjects will be Week 94.

Subjects who participate in the LTE period are to return to the study site to receive their first LTE dose approximately 4 weeks after their last dose in the placebo-controlled period of the study. A FU Visit will occur 18 weeks after the last LTE period dose. The timing of the final study visit for subjects participating in the LTE period will vary, since the EOT Visit for a subject who participates in the LTE period will occur at Week 338, or when the last subject has had his or her Week 182 Visit, whichever occurs first.

Subjects who discontinue treatment are to remain in the study, attend a FU Visit 18 weeks after the final dose, and immediately continue protocol-required tests and assessments at a subset of

the clinic visits (see Table 10 and Table 11) until the end of the study or until withdrawal of consent. Subjects who withdraw from the study are encouraged to return for FU assessments 18 weeks after their last dose of study treatment.

7.4. Study Stopping Rules

Biogen may terminate this study at any time, after informing Investigators. Biogen (or designee) will notify Investigators when the study is to be placed on hold, completed, or terminated.

Dosing may be terminated by the Sponsor at the recommendation of the IDMC, based exclusively on safety and tolerability data or following the futility analysis, or at the discretion of the Sponsor; therefore, there are no study-specific stopping rules defined in this protocol.

7.5. End of Study

The end of study is last subject, last visit. The EOT Visit for a subject who continues in the study will occur at Week 338, or when the last subject has had his or her Week 182 Visit, whichever occurs first.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at Screening or at the timepoint specified in the individual eligibility criterion listed:

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.
2. Aged 50 to 85 years old, inclusive, at the time of informed consent.
3. All women of childbearing potential and all men must practice highly effective contraception during the study and for 24 weeks after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 15.5.
4. Must have at least 6 years of education or work experience to exclude mental deficits other than MCI or mild AD.
5. Must have a positive amyloid PET scan. Previously obtained PET scan (within 12 months of Screening) is permissible for subjects not participating in the amyloid PET substudy. Previous PET scan images must be submitted to the central imaging vendor to confirm study inclusion criteria are met.
6. Must meet all of the following clinical criteria for MCI due to AD or mild AD according to NIA-AA criteria [Albert 2011; McKhann 2011], and must have:
   - A CDR global score of 0.5.
   - An RBANS score of 85 or lower indicative of objective cognitive impairment (based upon the Delayed Memory Index score).
   - An MMSE score between 24 and 30 (inclusive).
7. Apart from a clinical diagnosis of early AD, the subject must be in good health as determined by the Investigator, based on medical history and screening assessments.
8. Must consent to ApoE genotyping.
9. Has one informant/care partner who, in the Investigator's opinion, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally be available by phone to provide information to the Investigator and study staff about the subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study, and the use of the same informant/care partner for the duration of the study is encouraged.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening, or at the timepoint specified in the individual criterion listed:

Medical History

1. Any uncontrolled medical or neurological/neurodegenerative condition (other than AD) that, in the opinion of the Investigator, might be a contributing cause of the subject's cognitive impairment (e.g., substance abuse, vitamin B_{12} deficiency, abnormal thyroid function, stroke or other cerebrovascular condition, Lewy body dementia, fronto-temporal dementia, head trauma).
2. Clinically significant unstable psychiatric illness (e.g., uncontrolled major depression, uncontrolled schizophrenia, uncontrolled bipolar affective disorder) within 6 months prior to Screening.
3. Transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year prior to Screening.
4. Brain MRI performed at Screening (per centrally read MRI) that shows evidence of any of the following:
   - Acute or sub-acute hemorrhage.
   - Prior macrohemorrhage (defined as >1 cm in diameter on T2* sequence) or prior subarachnoid hemorrhage unless it can be documented that the finding is not due to an underlying structural or vascular abnormality (i.e., finding does not suggest subject is at risk of recurrent hemorrhage).
   - Greater than 4 microhemorrhages (defined as ≤1 cm in diameter on T2* sequence).
   - Cortical infarct (defined as >1.5 cm in diameter; irrespective of anatomic location).
   - >1 lacunar infarct (defined as ≤1.5 cm in diameter).
   - Superficial siderosis.
   - History of diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scale [Wahlund 2001].
   - Any finding that, in the opinion of the Investigator, might be a contributing cause of subject's dementia, might pose a risk to the subject, or might prevent a satisfactory MRI assessment for safety monitoring.
5. History of bleeding disorder or predisposing conditions, blood clotting or clinically significant abnormal results on coagulation profile at Screening, as determined by the Investigator.
6. Presence of diabetes mellitus that, in the judgment of the Investigator, cannot be controlled or adequately managed.

7. History of unstable angina, myocardial infarction, chronic heart failure (New York Heart Association Class III or IV), or clinically significant conduction abnormalities (e.g., unstable atrial fibrillation) within 1 year prior to Screening.
8. Clinically significant 12-lead ECG abnormalities, as determined by the Investigator.
9. Uncontrolled hypertension defined as: average of 3 systolic blood pressure [SBP]/diastolic blood pressure [DBP] readings >165 mmHg and/or >100 mmHg at Screening (blood pressure measurements exceeding these limits may be repeated as warranted by the Investigator, but values must be within the specified limits for the subject to be eligible for the study), or persistent SBP/DBP readings >180 mmHg and/or >100 mmHg 3 months prior to randomization (Day 1) that, in the opinion of the Investigator, are indicative of chronic uncontrolled hypertension.
10. History of malignancy or carcinoma. The following exceptions may be made after discussion with the Sponsor:
    - Subjects with cancers in remission more than 5 years prior to Screening.
    - Subjects with a history of excised or treated basal cell or squamous carcinoma of the skin.
    - Subjects with localized prostate cancer with treatment cycles that completed at least 6 months prior to Screening.
11. History of seizure within 10 years prior to Screening.
12. Indication of impaired liver function as shown by an abnormal liver function profile at Screening (e.g., repeated values of aspartate aminotransferase [AST] and alanine aminotransferase [ALT] $\geq 2 \times$ the upper limit of normal).
13. History or evidence of an autoimmune disorder considered clinically significant by the Investigator or requiring chronic use of systemic corticosteroids or other immunosuppressants.
14. Recent history (within 1 year of Screening) of alcohol or substance abuse as determined by the Investigator, a positive urine drug (due to non-prescription drug) or alcohol test at Screening, or use of cannabinoids (prescription or recreational).
15. Clinically significant systemic illness or serious infection (e.g., pneumonia, septicemia) within 30 days prior to or during Screening.
16. History of or known seropositivity for human immunodeficiency virus (HIV).
17. History of or positive test result at Screening for hepatitis C virus antibody or hepatitis B virus (defined as positive for both hepatitis B surface antigen AND hepatitis B core antibody).
18. History of severe allergic or anaphylactic reactions, or history of hypersensitivity to any of the inactive ingredients in the drug product (refer to the IB for information on the clinical formulation).

19. Any other medical conditions (e.g., renal disease) that are not stable or controlled, or, which in the opinion of the Investigator, could affect the subject's safety or interfere with the study assessments.

Medications

20. Any medications that, in the opinion of the Investigator, may contribute to cognitive impairment, put the subject at higher risk for AEs, or impair the subject's ability to perform cognitive testing or complete study procedures.
21. Use of allowed chronic medications at doses that have not been stable for at least 4 weeks prior to Screening Visit 1 and during Screening up to Study Day 1, or use of AD medications (including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine) at doses that have not been stable for at least 8 weeks prior to Screening Visit 1 and during Screening up to Study Day 1.
22. Use of medications with platelet anti-aggregant or anti-coagulant properties (the use of aspirin at a prophylactic dose [≤ 325 mg daily] is allowed).
23. Use of illicit narcotic medication.
24. Vaccinations within 10 days prior to randomization (Day 1).
25. Participation in any active immunotherapy study targeting Aβ unless documentation of receipt of placebo is available.
26. Participation in any passive immunotherapy study targeting Aβ within 12 months of Screening unless documentation of receipt of placebo is available.
27. Participation in any study with purported disease-modifying effect in AD within 12 months prior to Screening unless documentation of receipt of placebo is available. Subjects who developed ARIA-E during a previous disease-modifying trial should be excluded.
28. Participation in a previous study with aducanumab (subject is eligible if he/she did not receive active aducanumab).

Study Procedures

29. Contraindications to having a brain MRI (e.g., pacemaker; MRI-incompatible aneurysm clips, artificial heart valves, or other metal foreign body; claustrophobia that cannot be medically managed).
30. Contraindication to having a PET scan (e.g., inability to lie flat or still for the duration of the scan) or intolerance to previous PET scans (i.e., previous hypersensitivity reactions to any PET ligand or imaging agent, failure to participate in and comply with previous PET scans).
31. A negative PET scan result with any amyloid-targeting ligand within 6 months prior to Screening.
32. Have had or plan exposure to experimental radiation within 12 months prior to Screening such that radiodosimetry limits would be exceeded by participating in this study.

33. For subjects who consent to LP, any contraindications to having a LP (e.g., platelet count <100,000/μL, lumbar spine deformity). Any symptoms caused by or related to the optional LP during Screening must be resolved prior to randomization (Day 1). Subjects may still participate in the overall study even if participation in the optional LP portion is contraindicated.

Others

34. Female subjects who are pregnant or currently breastfeeding.
35. Previous participation in this study. Subjects who fail Screening will be permitted to be rescreened once at the Sponsor's discretion, except those who fail due to PET, MMSE, CDR global score >0.5, hepatitis B or C, or abnormal MRI findings. (Subjects who fail Screening due to a CDR global score of 0 may be rescreened; such subjects will be allowed to repeat the screening CDR assessment after 6 months.)
36. Subject currently living in an organized care facility with extensive intervention and/or support of daily living activities.
37. Blood donation (≥ 1 unit) within 1 month prior to Screening.
38. Inability to comply with study requirements.
39. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

8.3. Inclusion Criteria for Long-Term Extension Period

To be eligible to participate in the LTE period, subjects must meet the following eligibility criteria at Week 78:

1. Subject must have completed the placebo-controlled period of the study including the Week 78 Visit. Subject must have taken at least 14 doses and not have missed more than 4 consecutive doses, except for subjects whose dose was suspended due to ARIA (See Section 7.2.1). Subjects who do not meet these criteria may enter the LTE period only with Sponsor's approval.
2. The subject (or the subject's legally authorized representative) has the ability to understand the purpose and risks of the study and provide signed and dated informed consent (or assent) and authorization to use confidential health information in accordance with national and local subject privacy regulations.
3. Female subjects of childbearing potential and male subjects must practice highly effective contraception during the study and for 24 weeks after their last dose of study treatment.
4. Apart from a clinical diagnosis of AD, the subject must be in good health as determined by the Investigator, based on medical history.
5. Must have the ability to comply with procedures for protocol-related tests.

6. Has one informant/care partner who, in the Investigator's opinion, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally be available by phone to provide information to the Investigator and study staff about the subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study, and the use of the same informant/care partner for the duration of the study is encouraged.

8.4. Exclusion Criteria for Long-Term Extension Period

Subjects will be excluded from entering the LTE period if at Week 78 they have:

1. Any medical or psychiatric contraindication or clinically significant abnormality that, in the opinion of the Investigator, will substantially increase the risk associated with the subject's participation in and completion of the study.

9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

9.1. Screening and Enrollment

Subjects (or their legally authorized representative, where applicable) must provide informed consent before any screening tests are performed (see Section 17.3). During Screening, subjects can complete the neurocognitive scales (CDR, MMSE and RBANS) and ApoE genotyping to determine study eligibility under a separate, optional initial consent process. If the subject meets inclusion criteria for these 3 scales the full consent process must be completed prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process which would allow the administration of all screening assessments. When a subject signs the full informed consent form (ICF), that subject is considered to be enrolled in the study. ApoE genotyping may be performed at Visit 1 prior to other screening assessments.

Participating study sites are required to document all screened candidates initially considered for inclusion in this study. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log. The total study duration for each subject participating only in the placebo-controlled period will be approximately 102 weeks (approximately an 8-week screening period, 76 weeks of placebo or aducanumab dosing, and 18 weeks of FU).

9.2. Randomization and Registration of Subjects

Subjects will be registered at the Screening Visit and randomized only after all baseline assessments have been completed and the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. No subject may begin treatment prior to assignment of a unique identification number (registration) and randomization. Any subject identification numbers or randomization schedule assignments that are assigned will not be reused even if the subject does not receive treatment. Rescreened subjects will be assigned a new number.

Subjects will be randomized to receive aducanumab low dose:aducanumab high dose:placebo in a 1:1:1 ratio. The randomization will be stratified by site and ApoE ε4 status (carrier or non-carrier). Subjects randomized to placebo at the start of the placebo-controlled period will also be randomized to receive dose-blinded aducanumab (low dose:high dose, 1:1 ratio) for the LTE period and randomization will be stratified by subject ApoE ε4 carrier status. Treatment group assignments for the placebo-controlled period and the LTE period will be assigned at Study Day 1. Enrollment will be monitored, via the IRT, such that the population of subjects with mild AD represents a small percentage of the total enrolled in the trial. Subjects who withdraw from the study may not be replaced.

Refer to the Study Reference Guide for details on registration and randomization.

9.3. Blinding Procedures

This study consists of a randomized, double-blind, placebo-controlled period, followed by a dose-blinded LTE period with all subjects receiving aducanumab.

For the double-blinded placebo-controlled period, all study staff who conduct subject assessments will be blinded to the subject treatment assignments. The rating HCPs should remain blinded to treatment assignment as well as subject care management and only have access to the information necessary to carry out their responsibilities as detailed in Section 4.3.1. As a placebo match is not provided for the study, unblinded pharmacy staff are required to manage all aspects of study treatment receipt, dispensing, and preparation. To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Biogen or its representatives, except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded IQVIA or Biogen safety staff.

For the LTE period, the dose information must remain restricted. The rating and treating HCP should remain blinded to treatment assignment and only have access to the information necessary to carry out their responsibilities as detailed in Section 4.3.1. To maintain the study blind, it is imperative that dose information is not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Biogen or its representatives, except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded IQVIA or Biogen safety staff.

10. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

A subject *must* permanently discontinue study treatment for any of the following reasons:

- The subject develops any of the following:
  - ARIA-E accompanied by serious clinical symptoms except for "other medically important event" as defined in Table 13.
  - Symptomatic ARIA-H (microhemorrhages) with serious clinical symptoms except for "other medically important event" as defined in Table 14.
  - Symptomatic ARIA-H (superficial siderosis) with or serious clinical symptoms except for "other medically important event" as defined in Table 15.
  - ARIA-H with ≥ 10 microhemorrhages and/or >2 focal areas of superficial siderosis.
  - Any new incident macrohemorrhage (defined as >1 cm in diameter on T2* sequence).

  See Section 7.2.1 for full details regarding discontinuation and dose reduction due to ARIA-E or ARIA-H.
- The subject becomes pregnant. Study treatment must be discontinued immediately and pregnancy must be reported according to the instructions in Section 15.4.1.
- The subject withdraws consent to continue study treatment.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment or unblinding of the subject's treatment assignment.
- The subject experiences an AE that does not resolve or requires continued treatment that meets exclusionary criteria (see Section 11.5.1.2).
- The subject experiences a severe infusion reaction.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Investigator or Sponsor for noncompliance.

The reason for discontinuation of study treatment must be recorded in the subject's case report form (CRF).

A subject who discontinues treatment is to remain in the study, attend a FU Visit 18 weeks after the final dose, and immediately continue protocol-required tests and assessments at a subset of the clinic visits (see Table 10 and Table 11) until the end of the study per the schedule of events or until the subject withdraws consent.

10.2. Withdrawal of Subjects From Study

Subjects must be withdrawn from the study for any one of the following reasons:

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator or Sponsor.

Note: A subject who discontinues study treatment will not be automatically withdrawn from the study, regardless of the number of doses missed. The subject is to remain in the study, and continue with a FU Visit 18 weeks after the final dose, and protocol-required tests and assessments at a subset of the clinic visits (see Table 10 and Table 11) until the end of the study or until the subject withdraws consent.

The reason for the subject's withdrawal from the study must be recorded in the subject's CRF.

Subjects who are withdrawn from the study after receiving ≥ 1 doses of study treatment should complete the EOT Visit after the reason for withdrawal is identified. For such subjects, efficacy assessments specified at the EOT Visit are not required if the subject discontinues treatment within 3 months of the previous efficacy assessment visit and no significant changes in cognitive status are suspected by the Investigator; The site should notify the sponsor in such cases. Subjects who are withdrawn from the study are also to return to the site for a FU Visit 18 weeks after receiving their last dose of study treatment.

11. STUDY TREATMENT USE

11.1. Regimen

Refer to and follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

Please see Section 4.2 (Schedule of Events) for the study treatment infusion schedule during the placebo-controlled and LTE periods of the study.

Aducanumab is to be administered by IV infusion following dilution into saline. See Section 12 for details of aducanumab study treatment.

11.1.1. Aducanumab

The Sponsor will provide aducanumab to study sites.

11.1.2. Placebo

Placebo [redacted] sodium chloride) will be supplied by the study site.

11.2. Modification of Dose and/or Treatment Schedule

Refer to Section 7.2.1 (dose suspension) and Section 7.2.2 (infusion interruption). Doses should be administered at least 21 days apart. If the dosing interval cannot be met, the dose administration should be assessed by the study medical monitor.

11.3. Precautions

Not applicable.

11.4. Compliance

Compliance with treatment dosing is to be monitored and recorded by unblinded site staff.

11.5. Prior and Concomitant Therapy and Procedures

11.5.1. Prior and Concomitant Therapy

Prior AD medication use within the 12 months prior to Screening will be captured.

A concomitant therapy is any drug or substance administered between the informed consent and until the subject's final clinic visit (including the FU Visit).

No premedication (e.g., anti-allergy drugs, antipyretic analgesics) should be used prior to the start of study treatment infusion unless discussed with the study medical monitor in advance.

11.5.1.1. Allowed Concomitant Therapy

- Medications for chronic conditions are allowed at a stable dose during the study as long as the subject has been stable on the medication(s) for at least 4 weeks prior to Screening Visit 1 and during the screening period.
- Symptomatic therapies for AD, including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine, are allowed provided that subjects are receiving a stable dose for at least 8 weeks prior to Screening Visit 1 and during the screening period and that they stay on a stable dose while in the study.
- Vaccinations with live or attenuated vaccines are allowed during the study. Administration of any vaccination/booster should not be given < 10 days prior to any dosing visit and for 10 days after a dosing visit.

11.5.1.2. Disallowed Concomitant Therapy

- Medications with platelet anti-aggregant or anti-coagulant properties, except the use of aspirin at a dose of ≤ 325 mg per day.
- Non-prescription narcotic medication.
- Immunosuppressive drugs (including systemic corticosteroids). Local corticosteroids (including inhaled and topical corticosteroids) are allowed; certain systemic corticosteroids may be permitted at the Sponsor's discretion.
- Parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange, and plasmapheresis.
- Any investigational drug.

Subjects should be instructed to continue the medications that they were receiving at enrollment without any changes (see allowed concomitant therapy above) and avoid starting any new medications or herbal preparations during the study period, as it may confound the results of the study. However, medically indicated medication or treatment should not be withheld. Subjects should inform the Investigator of any changes in medication. The change should be reviewed by the Investigator and the study medical monitor to determine whether the subject's study treatment should be suspended. Medications used to treat AEs would not result in automatic permanent study treatment discontinuation. However, as noted in Section 10.1, if a subject requires continued use of a disallowed therapy, the subject must permanently discontinue study treatment. The Sponsor may be consulted if required.

Subjects should have an unscheduled visit for a change in AD medication, and all clinical assessments for the primary and secondary objectives should be performed prior to the change in medication.

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, routine colonoscopy, bacterial cultures)

performed between the time the subject is enrolled in the study and until the subject's final clinic visit (including FU Visit), unless the subjects is being followed for study-related toxicity.

The use of concomitant therapies or procedures defined above must be recorded on the subject's CRF. AEs related to administration of these therapies or procedures must be documented on the appropriate AE CRF.

11.6. Continuation of Treatment

No further provisions are made for access to the study treatment. If aducanumab is proven to be beneficial, all regulatory requirements regarding poststudy access will be met.

12. STUDY TREATMENT MANAGEMENT

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Study treatment vials are for one-time use only; any study treatment remaining in the vial must not be used for another subject.

12.1. Aducanumab

Research Name: BIIB037

Generic Name: Aducanumab

Trade Name(s): Not applicable

Synonyms: Fully human, IgG_1, anti-Aβ monoclonal antibody

Aducanumab is a recombinant human antibody expressed in a Chinese hamster ovary cell line, purified to a high degree of purity and formulated as a liquid. Aducanumab is an IgG_1 consisting of 2 heavy and 2 kappa light chains connected by inter-chain disulfide bonds. Aducanumab has 1 carbohydrate moiety linked to Asn-304. Aducanumab is purified from the media and formulated as a liquid.

Aducanumab is supplied as a liquid drug product containing either:

- aducanumab [redacted] (excipients: sodium citrate, citric acid, L-arginine hydrochloride, and polysorbate-80)

  or

- aducanumab [redacted] (excipients: L-histidine hydrochloride, L-histidine free base, L-arginine hydrochloride, L-methionine, and polysorbate-80)

The concentration for each vial (either [redacted] appears on the label. Aducanumab is manufactured in accordance with Good Manufacturing Practices.

The contents of the label will be in accordance with all applicable regulatory requirements. Aducanumab should not be used after the expiration date.

12.1.1. Aducanumab Preparation

The individual preparing aducanumab should carefully review the instructions provided in the DHA.

Aducanumab is to be administered by IV infusion following dilution into saline.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the vials or drug it should not be used. The vial in question should be saved at the study site, and the problem immediately reported to Biogen.

12.1.2. Aducanumab Storage

Study treatment must be stored in a secure location. Aducanumab is to be stored at 2°C to 8°C (36°F to 46°F), in a locked storage container with limited access. Aducanumab should be protected from light, protected from freezing, and should not be shaken. If administration of the prepared aducanumab is delayed for more than 4 hours, then it should be kept at 2°C to 8ºC until use. If administration of the prepared aducanumab is delayed for more than 24 hours, it must be discarded. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

12.1.3. Aducanumab Handling and Disposal

The Investigator must return all used and unused vials of aducanumab as instructed by Biogen (or its designee), unless approved for onsite destruction.

If any aducanumab supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from Biogen by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Biogen must be notified in writing of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. Aducanumab Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), and accounts of any study treatment accidentally or deliberately destroyed.

Unless otherwise notified, all vials both used and unused, must be saved for study treatment accountability. By the end of the study reconciliation must be made between the amount of aducanumab supplied, dispensed, and subsequently destroyed or returned to Biogen. A written explanation must be provided for any discrepancies.

12.2. Placebo

The placebo CCI sterile sodium chloride for injection) will be provided by the site in the form of 100 mL saline IV bags.

12.3. Additional Protocol-Designated Products

Refer to the DHA for infusion-related supply specifications.

To confirm amyloid pathology at Screening, PET scans will be performed using Amyvid™ (^{18}F-florbetapir), Vizamyl™ (^{18}F-flutemetomol), or Neuraceq™ (^{18}F-florbetaben). For those subjects participating in the amyloid PET substudy, Screening and FU scans must be performed

using Amyvid and for subjects participating in the PET substudy in Japan, Vizamyl (^{18}F-flutemetomol) may also be used. For details on PET imaging ligands, including tau PET, refer to the procedural manual for PET.

13. EFFICACY, PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS

Refer to Section 4.2 for the timing of assessments.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of aducanumab:

- CDR
- MMSE
- ADAS-Cog 13
- ADCS-ADL-MCI
- NPI-10

It is recommended that clinical assessments be performed at the same time of day for subjects during their study visits.

Some tests will require the informant/care partner to participate and answer questions regarding the subject's daily activities and cognitive capabilities.

The recommended order of administration of the clinical assessments is described in the Study Reference Guide.

13.2. Pharmacokinetic Assessments

Serum concentrations of aducanumab will be measured using a validated assay.

13.3. Pharmacodynamic Assessments

The following tests will be performed to assess the PD properties of aducanumab:

- Serial measurement of amyloid plaque burden in certain areas of the brain as measured by amyloid PET (in a subset of approximately 400 subjects participating in the amyloid PET cohort).

  Only sites with capabilities of performing ^{18}F-florbetapir PET will be allowed to perform this assessment. Investigator participation in this part of the study is optional and contingent upon approval by his/her ethics committee (EC) or institutional review board (IRB). If the Investigator is not participating or the test is not approved by his/her EC/IRB, the relevant section of the ICF will not be applicable to that site.

  Subject participation in this part of the study is optional at participating sites. Informed consent must be recorded in the CRF. Detailed PET scanning protocols will be described in a separate procedural manual for PET. Approximately 400 subjects are expected to participate in the amyloid PET substudy.

- Whole brain volume, hippocampal volume, ventricle volume, and cortical gray matter volume measured by MRI.

  Detailed MRI scanning protocols will be described in the procedural manual for MRI.

- Functional connectivity as measured by tf-fMRI (in a subset of sites and subjects, where available).

  Only sites with capabilities of performing tf-fMRI will be allowed to perform this assessment. Detailed tf-fMRI scanning protocols will be described in the procedural manual for MRI.

- Cerebral blood flow as measured by ASL-MRI (in a subset of sites and subjects, where available).

  Only sites with capabilities of performing ASL-MRI will be allowed to perform this assessment. Detailed ASL-MRI scanning protocols will be described in the procedural manual for MRI.

- Disease- or treatment-related blood and CSF biomarkers. Subject participation in CSF collection is optional (see Section 13.4.1).

- Tau PET signal (in a subset of sites and subjects, where available).

13.4. Additional Assessments

13.4.1. CSF Biomarkers (Lumbar Puncture Test)

An optional CSF collection will be conducted at sites. Investigator participation in this part of the study is optional and contingent upon approval by the site's EC/IRB. If the Investigator is not participating or the test is not approved by the site's EC/IRB, the relevant section of the ICF will not be applicable to that site.

Subject participation in the LP test is optional at participating sites. Informed consent must be recorded in the CRF.

Analyses of CSF samples will include, but are not limited to, the following:

- Disease- or treatment-related biomarker levels (e.g., amyloid and tau proteins).
- Cell count and differential (to be conducted by the local laboratory).
- Total protein (to be conducted by the central laboratory).

Four LPs are to be performed (1 at Screening, 1 in the placebo-controlled period, and 2 in the LTE period). CSF collection at Screening using study-specific procedures is preferred; however, if a CSF sample has been obtained within 3 months prior to Screening, this sample may be used in lieu of requiring an LP at Screening. Any symptoms caused by or related to the LP must be resolved or stabilized, in the opinion of the Investigator, prior to infusion. Vital signs will be obtained before the LP at each visit for subjects participating. Guidance on LPs will be provided in the Study Reference Guide.

13.4.2. ApoE Genotyping

Whole blood samples for deoxyribonucleic acid (DNA) ApoE genotyping will be collected from all subjects at the Screening Visit.

13.4.3. Optional DNA Test

Where local regulations and ethics committee approval allow, an optional DNA sample will be collected for future genetic analysis. This optional 1-time blood collection requires additional consent from the subject.

Genetic polymorphism in genes encoding drug targets or the downstream pathways, as well as proteins that impact drug absorption, distribution, metabolism, and elimination, may affect the safety and efficacy of aducanumab.

In the event of an unusual response or observation of unexplained AEs, DNA samples may be used to determine if there are any pharmacogenetic associations with drug response.

In the future, as the understanding of AD, disease-modifying AD treatments and/or aducanumab, additional genetic analyses may be warranted to refine the knowledge of the molecular basis of the disease and the drug response and to advance the development of novel therapeutics. The samples may also be used to understand the biology of other diseases and traits of interest to Biogen.

The DNA samples will be coded with the subject's identification number and stored for 15 years or a duration dictated by local, national, or regional laws or regulations. No genotyping or genetic data will be provided to the subject. Subjects may withdraw consent and request to have their sample destroyed at any time and no further genetic data will be generated; any data already generated will not be destroyed.

13.4.4. Health Outcomes Assessments

The following assessments will be performed to evaluate the effect of aducanumab in subjects and caregivers:

- EQ-5D (SR)
- EQ-5D (IR-S)
- EQ-5D (IR-I)
- mPDQ-20
- CAM

Some tests will require the informant/care partner to participate and answer questions regarding the subject's daily activities and cognitive capabilities.

The recommended order of administration of the clinical assessments is described in the Study Reference Guide.

13.5. Future Scientific Research Assessments

In subjects who provide additional optional consent, serum, plasma, CSF and ribonucleic acid samples may be collected and residual samples may be stored for future, unspecified, exploratory biomarker analysis. Subjects will sign a separate, written ICF if they agree to this sample collection and/or to their samples being used in this way.

The samples collected may be utilized to identify or verify putative, prognostic, and predictive markers associated with disease and markers of therapeutic response to treatment, and/or to develop diagnostic and analytical tests. Background and dynamic clinical disease characteristics and associated biomarker data may be utilized to predict subsequent disease worsening (severity), identify high-risk patient subgroups, and identify predictors of response to treatment.

14. SAFETY ASSESSMENTS

See Section 4.2 for the timing of assessments.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of aducanumab:

- AE and SAE monitoring.
- Physical examination, including height and weight.
- Neurological examination.
- Vital signs (body temperature, heart rate, SBP, DBP, and respiratory rate).
- 12-lead ECG.
- Brain MRI.
- Concomitant medication, therapy, and procedure monitoring.
- MOCA (for ARIA monitoring and management).
- Columbia Suicide Severity Rating Scale (C-SSRS).

14.2. Laboratory Safety Assessments

The following laboratory assessments will be performed to evaluate the safety profile of aducanumab

- Hematology: complete blood count with differential and platelet count, and absolute neutrophil count.
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, ALT, AST, lactate dehydrogenase, gamma-glutamyl-transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, and potassium.
- Urinalysis: color, specific gravity, pH, protein, glucose, blood, ketones, and microscopic examination (if abnormal).
- Serum and urine pregnancy test for women of childbearing potential only.
- Coagulation, virology (including HIV at the Investigator's discretion after consideration of risk factors), HbA_{1c}, and alcohol/drug screen at Screening.

14.3. Immunogenicity Assessments

Presence of serum anti-aducanumab will be determined using a validated assay. A standard 3-tier antidrug antibody (ADA) approach will be used (i.e., screening assay, confirmatory assay, and titration assay). Additional characterization of the immune response may be performed.

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject or his/her legally authorized representative must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Determination of whether an abnormal laboratory value meets the definition of an AE will be made by the Investigator. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE.
- A laboratory test result that requires the subject to receive specific corrective therapy.
- A laboratory abnormality that the Investigator considers to be clinically significant.

Pre-treatment, nonserious AEs that occur within 48 hours after receipt of a ligand will be captured by the sites on the AE form.

15.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

15.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject is hospitalized. The study site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
  - If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 15.1.2 is met.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2.
- The relationship of the event to study treatment as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment.

Relationship of Event to Study Treatment	
Not related	An AE will be considered "not related" to the use of the investigational drug if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include but are not limited to: the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of the investigational drug if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of an alternative explanation for the AE.

15.2.3. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by Biogen according to the IB for aducanumab.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and the subject's final clinic visit (including FU Visit) is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment. Pre-treatment, nonserious AEs that occur within 48 hours after receipt of a ligand will be captured by the sites on the AE form.

15.3.2. Adverse Events of Special Interest

ARIA-E and ARIA-H are considered AEs of special interest and will be entered on the Adverse Event of Special Interest CRF within 72 hours following the receipt of abnormal MRI findings from the central MRI reader.

AE reporting for ARIA-E and ARIA-H will be based on the following centrally read MRI sequences: fluid attenuated inversion recovery/T2 for ARIA-E and T2*/gradient echo for ARIA-H.

If the event qualifies as an SAE an SAE form should be submitted per the guidelines in Section 15.3.4. Investigators should include a copy of the centrally read MRI report when submitting the SAE form to IQVIA Lifecycle Safety.

15.3.3. Serious Adverse Events

Any SAE experienced by the subject between signing of the ICF and the subject's final clinic visit (including FU Visit) will be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to Biogen (or designee) within 24 hours as described in Section 15.3.4. This also applies to SAEs that occur after administration of the ligand. FU information regarding an SAE also must be reported with 24 hours.

Events occurring after the subject's final clinic visit (including FU Visit) should be reported to Biogen only if the Investigator considers the SAE related to study treatment.

Any SAE that is ongoing when the subject completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

15.3.4. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify IQVIA Lifecycle Safety within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any SAE that occurs between the time that the subject has signed the ICF and the subject's final clinic visit (including FU Visit) must be reported to IQVIA Lifecycle Safety within 24 hours of the study site staff becoming aware of the event. Thereafter, the event should be reported only if the Investigator considers it related to study treatment.

A report ***must be submitted*** to IQVIA Lifecycle Safety regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject has received study treatment
- The severity of the event

- The relationship of the event to study treatment

To report initial or FU information on an SAE, fax or email a completed SAE form. Refer to the Study Reference Guide for country-specific IQVIA Lifecycle Safety fax numbers or email PPD

15.3.4.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to IQVIA Lifecycle Safety. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.5. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen to be related to the study treatment administered.

Appropriate personnel in Biogen Safety and Benefit Risk (SABR) will unblind SUSARs for the purpose of regulatory reporting. Biogen or designee will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Biogen or designee will submit SUSARs to Investigators in a blinded fashion.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

Subjects should not become pregnant or impregnate their partners during the study and for 24 weeks after their last dose of study treatment. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy occurring in a female subject by faxing the appropriate form to IQVIA Lifecycle Safety within 24 hours of the study site staff becoming aware of the pregnancy at the SAE reporting fax number provided in the study reference manual. The Investigator or study site staff must report the outcome of the pregnancy to IQVIA Lifecycle Safety.

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period.

15.4.2. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on an Overdose form and faxed to IQVIA Lifecycle Safety within 24 hours of the site becoming aware of the overdose. An overdose must be reported to IQVIA Lifecycle Safety even if the overdose does

not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed to IQVIA Lifecycle Safety). All study treatment-related dosing information must be recorded on the dosing CRF.

15.4.3. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator (or designee) should contact the IQVIA 24-hour emergency medical support number. Refer to the Study Reference Guide's Official Contact List for complete contact information.

15.4.3.1. Unblinding for Medical Emergency

In this study, emergency decoding will be made available to the Investigator and designated personnel at Biogen through IRT.

In a medical emergency when knowledge of the subject's treatment assignment may possibly influence the subject's clinical care, the Investigator may access the subject's treatment assignment by IRT. However, prior to unblinding, the Investigator can contact the IQVIA 24-hour emergency medical support number at PPD

The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, nor to personnel involved with the analysis and conduct of the study.

15.5. Contraception Requirements

For the purposes of this study, women of childbearing potential are defined as all women physiologically capable of becoming pregnant, UNLESS they meet one of the following conditions:

- Postmenopausal
  - 12 months of natural (spontaneous) amenorrhea without an alternative medical cause or 6 weeks after surgical bilateral oophorectomy with or without hysterectomy.
- Post hysterectomy.
- Female surgical sterilization (e.g., bilateral tubal ligation).

For the purposes of this study, highly effective contraception is defined as use of 1 of the following:

- For females of childbearing potential:
  - Established use of oral, injected, or implanted hormonal methods of contraception.
  - Placement of an intrauterine device or intrauterine system

  - Barrier methods of contraception with use of a spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide.
  - Male sexual partners underwent surgical sterilization with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate.

- For males:
  - Vasectomy with negative semen analysis at FU.
  - Use of condoms with spermicide.
  - Female sexual partners who underwent surgical sterilization (e.g., bilateral tubal ligation), are postmenopausal, are post-hysterectomy, or are using highly effective contraception as listed above for female subjects.

  For males and females of childbearing potential:

  True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies and FU on the outcome of the pregnancy in female subjects.
- Complete an SAE form for each SAE and fax it to Biogen (or designee) within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE FU information actively and persistently. FU information must be reported to Biogen (or designee) within 24 hours of the study site staff becoming aware of new information.

- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE FU information, if possible, until the event has resolved or become stable.
- Report SAEs to local EC/IRBs, as required by local law.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor (IQVIA) is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen (or designee) is to notify all appropriate regulatory authorities, central EC/IRBs, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Demography and Baseline Disease Characteristics

Demographics and baseline data will be summarized by treatment group with summary statistics (mean, standard deviation [SD], median, and range) or with frequency distributions.

16.2. Efficacy and Pharmacodynamics

16.2.1. Analysis Population

The intent-to-treat (ITT) population, defined as all subjects who were randomized and received at least 1 dose of study treatment (aducanumab or placebo), will be used for the efficacy analyses. Subjects will be analyzed in the groups to which they were randomized.

16.2.2. Methods of Analysis

16.2.2.1. General Considerations

Summary statistics will be presented. For continuous endpoints, summary statistics will generally include: number of subjects with data, mean, standard deviation, median, and range. For categorical endpoints, this will generally include: number of subjects randomized or dosed, number with data, and the percent of those with data in each category. Statistical testing for efficacy endpoints will be made between each aducanumab dose (high and low) and placebo. All statistical tests will be 2-sided.

16.2.2.2. Aducanumab Doses to be Evaluated

The following aducanumab doses as compared with placebo will be evaluated:

- Aducanumab high-dose (10 mg/kg in ApoE ε4 [including 6 mg/kg for subjects enrolled under protocol versions prior to Version 4 who do not have the opportunity to uptitrate to 10 mg/kg prior to completing Week 78 of the study] and 10 mg/kg in ApoE ε4 non-carriers).
- Aducanumab low-dose (3 mg/kg in ApoE ε4 carriers and 6 mg/kg in ApoE ε4 non-carriers).

In the event that the maximum dose (10 mg/kg) is terminated after the start of the study (Section 5.3.2) the definition of aducanumab high dose and aducanumab low dose will be modified as shown in Table 17. The dosing modification will be entirely based on interim analysis of outcomes that are independent of, and uninformative about, the treatment-related efficacy effect. Control of Type I error rate is thus maintained without a statistical adjustment for such adaptations [Chow and Chang 2011].

Table 17: Treatment Groups in the Event of High Dose Group Termination

High Dose Group(s) Terminated	Definitions of Revised Treatment (Low/High Dose) Groups for Comparison
ApoE ε4 carrier high-dose group (10 mg/kg) [including 6 mg/kg for subjects enrolled under versions prior to Version 4 who do not have the opportunity to uptitrate to 10 mg/kg prior to completing Week 78 of the study]	Low: ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg High: ApoE ε4 carrier 3 mg/kg and non-carrier 10 mg/kg
ApoE ε4 non-carrier high-dose group (10 mg/kg)	Low: ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg High: ApoE ε4 carrier 10 mg/kg and non-carrier 6 mg/kg
ApoE ε4 carrier high-dose group (10 mg/kg) AND ApoE ε4 non-carrier high-dose group (10 mg/kg)	ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg

16.2.2.3. Considerations for Multiple Comparison Adjustments

A sequential (closed) testing procedure will be used to control the overall Type I error rate due to multiple comparisons for the primary endpoint. The order of treatment comparisons is as follows: aducanumab high-dose versus placebo and aducanumab low-dose versus placebo. All comparisons after the initial comparison with $p > 0.05$ will not be considered statistically significant.

Secondary endpoints have been rank prioritized, in the order shown in Section 6. In order to control for a Type I error for the secondary endpoints, a sequential closed testing procedure will be used and will include both the order of the secondary endpoints and treatment comparisons. Specifically, for each of the secondary endpoints, a sequential (closed) testing procedure, as for the primary endpoint, will be used to control the overall Type I error rate due to multiple treatment comparisons. If statistical significance is not achieved for 1 or 2 comparisons, all endpoint(s) of a lower rank will not be considered statistically significant for 1 or 2, respectively.

16.2.2.4. Analysis of the Primary Endpoint

The population for the primary endpoint analysis will be subjects in the ITT population. A mixed model repeated measures (MMRM) model will be used as the primary analysis to analyze change from baseline CDR-SB using fixed effects of treatment, time, treatment-by-time interaction, baseline CDR-SB, baseline CDR-SB by time, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE ε4 status.

16.2.2.5. Analysis of the Secondary Endpoints

16.2.2.5.1. Change From Baseline to Week 78 in MMSE

The population for the analysis will be subjects in the ITT population. A MMRM model will be used as the primary analysis to analyze change from baseline MMSE using fixed effects of treatment, time, treatment-by-time interaction, baseline MMSE value, baseline MMSE by time interaction, AD symptomatic medication use at baseline, region, and laboratory ApoE ε4 status

16.2.2.5.2. Change From Baseline to Week 78 in ADAS-Cog 13

The population will be subjects in the ITT population. An MMRM model will be used as the primary analysis to analyze change from baseline ADAS-Cog 13 using fixed effects of treatment, time, treatment-by-time interaction, baseline ADAS-Cog 13, baseline ADAS-Cog 13 by time interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE ε4 status.

16.2.2.5.3. Change From Baseline to Week 78 in ADCS-ADL-MCI

The population will be subjects in the ITT population. An MMRM model will be used as the primary analysis to analyze change from baseline ADCS-ADL-MCI using fixed effects of treatment, time, treatment-by-time interaction, baseline ADCS-ADL-MCI, baseline ADCS-ADL-MCI by time interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE ε4 status.

16.2.2.6. Tertiary Endpoints Analysis

16.2.2.6.1. Placebo-Controlled Period

Where appropriate, an MMRM model will be used as the primary analysis to analyze change from baseline using fixed effects of treatment, time, treatment by time interaction, baseline value, baseline value by time interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE ε4 status.

Otherwise, an analysis of covariance may be used to analyze these exploratory endpoints or descriptive summary statistics may be presented.

16.2.2.6.2. Long-Term Extension Period

The endpoints for the LTE period are change from baseline over the placebo-controlled and LTE periods of the study. Analyses will be presented by treatment group in the LTE period using the placebo-controlled period baseline. Details of the analyses will be prespecified in the statistical analysis plan (SAP).

16.3. Pharmacokinetics

16.3.1. Analysis Population

The population for PK analysis is defined as all subjects who were randomized, were dosed with study treatment, and had at least 1 measurable aducanumab concentration in serum.

16.3.2. Method of Analysis

The serum concentrations and PK parameters of aducanumab will be summarized descriptively.

16.4. Additional Exploratory Analyses

Results of analyses of additional exploratory endpoints, if performed, may be documented separately, and details related to the analyses will not be described in the protocol.

16.5. Safety

16.5.1. Analysis Population

The safety population is defined as all subjects who were randomized and received at least 1 dose of study treatment (including placebo and aducanumab).

16.5.2. Methods of Analysis

All AEs, laboratory data, ECG, neurological and physical examinations and vital signs will be evaluated for safety.

16.5.2.1. Adverse Events

Only treatment-emergent adverse events (TEAEs) will be presented in the summary tables. Treatment emergent is defined as having an onset date that is on or after the start of study treatment, or as worsening after the start of study treatment.

Incidence of TEAEs will be summarized by treatment groups, overall, by severity, and by relationship to study treatment for the placebo-controlled period and up to 5 years of LTE period. The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

16.5.2.2. Clinical Laboratory Results

Laboratory data will be summarized using shift tables. Shifts from baseline to high/low status for hematology and blood chemistry parameters, and shifts from baseline to high/positive status for urinalysis will be presented. In addition, the shift from baseline to the maximum post-baseline value and the shift from baseline to the minimum post-baseline status will be presented for each laboratory test by treatment group. Also, summaries of laboratory values categorized based on common toxicity criteria grade will be created. Summary statistics for actual values and change from baseline will also be presented for quantitative laboratory data.

16.5.2.3. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities.

16.5.2.4. ECG

The number and percentage of subjects with shifts to categorical values (abnormal not AE, or abnormal AE) will be summarized by treatment group.

16.5.2.5. Columbia Suicide Severity Rating Scale

The C-SSRS data will be summarized by treatment group.

16.6. Immunogenicity Data

16.6.1. Analysis Population

The analysis population for immunogenicity is defined as all subjects in the safety population who have at least 1 post-dose sample evaluated for immunogenicity.

16.6.2. Methods of Analysis

Anti-aducanumab serum antibodies will be summarized using shift tables.

16.7. Interim Analyses

16.7.1. Interim Futility Analysis

An interim analysis for futility of the primary endpoint will occur after approximately 50% of the subjects have completed the Week 78 Visit (or discontinued). In order to maintain the treatment blind, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim futility analysis. This independent group will present the unblinded interim analysis to the IDMC. The IDMC may recommend terminating the study for futility if it is evident that the efficacy of aducanumab is unlikely to be achieved.

The futility criteria will be discussed in detail in the SAP.

16.7.2. Interim Superiority Analysis

An interim analysis for superiority may be performed after approximately 50% of the subjects have completed the Week 78 Visit (or discontinued). The O'Brien-Fleming boundary approach will be used for the analysis. In order to maintain the treatment blind in the event of this interim analysis, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim superiority analysis. The independent group will present the unblinded interim analysis to the IDMC. The aim of this interim analysis is to allow the possibility to demonstrate treatment effect early. The analysis will be discussed in detail in the SAP.

16.8. Sample Size Considerations

The study's sample size is based, in part, on results from a protocol-specified interim analysis from Study 221AD103, which included 1-year data from 1, 3, and 10 mg/kg treatment groups.

A sample size of 450 subjects per treatment group (1350 in total) was planned to have approximately 90% power to detect a true mean difference of 0.5 in change from baseline CDR-SB at Week 78 between the 2 treatment groups. This power calculation was based on a 2-sided t-test assuming equal variance with a final significance level of 0.05, an SD of 1.92, and a drop-out rate of 30%. The SD estimate of 1.92 for Week 78 reflected a 39% increase over the SD from the protocol-specified interim analysis of 1-year data.

The assumed true mean difference of 0.5 between the 2 treatment groups represents an approximately 25% reduction in the placebo mean change from baseline at Week 78 if the placebo mean change is estimated to be 2.

As defined in the prior versions of the protocol, the sample size for this study (and for the identically designed Study 221AD302) was reassessed in a blinded manner approximately 3 months before enrollment completion. At the time of this reassessment (November 2017), about 10.6% of the data was available on the primary endpoint from Study 221AD301 and Study 221AD302 combined; based on the pooled blinded data (i.e., treatment groups combined) from the 2 studies, the SD for the primary endpoint was estimated. As a result of this analysis, the sample size has been adjusted from 1350 to 1605 (450 to 535 per treatment) to assure adequate power to detect a mean treatment effect of 0.5.

17. ETHICAL REQUIREMENTS

Biogen, IQVIA, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated.

17.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

17.2. Ethics Committee/Institutional Review Board

The Investigator must obtain EC/IRB approval of the protocol, ICF, and other required study documents prior to starting the study. Biogen will submit documents on behalf of the investigational sites worldwide in compliance with local requirements.

If the Investigator makes any changes to the ICF, Biogen must approve the changes before the ICF is submitted to the EC. A copy of the approved ICF must be provided to Biogen. After approval, the ICF must not be altered without the agreement of the relevant EC and Biogen.

It is the responsibility of the Investigator(s) to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

Biogen must receive a letter documenting EC/IRB approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the EC/IRB at required intervals and not less than annually.

At the completion or termination of the study, the investigational site must submit a close-out letter to the EC/IRB and Biogen.

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations. Subjects can complete the neurocognitive scales (CDR, MMSE, and RBANS) as well as ApoE genotyping as an initial optional screening under a separate consent process. If the subject meets inclusion criteria for these 3 scales, the full consent process must be completed prior to the administration of further screening assessments.

Subjects may also proceed directly to the full consent process that would allow the administration of all screening assessments.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject (or the subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

Subjects will be informed that their race and/or ethnicity will be collected and will be used during analysis of study results (only in countries where permitted by local law/regulation).

A copy of the signed and dated ICF must be given to the subject, caregiver and/or legally authorized representative. The signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the subject's medical record.

17.4. Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., Protected Health Information authorization in North America).

The subject will not be identified by name in the CRF or in any study reports and these reports will be used for research purposes only. Biogen, its partner(s) and designee(s), EC/IRBs, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

During the study, subjects' race and/or ethnicity will be collected (only in countries where permitted by local law/regulation). These data may be used in the analysis of the safety, efficacy, and/or pharmacokinetic profile of the study treatment. It is unknown if the potency or effects of the study treatment are influenced by race or ethnicity.

17.5. Compensation for Injury

Biogen maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in Biogen or its partner[s]) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

Biogen will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by Biogen. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

During and/or after completion of the study, quality assurance officers named by Biogen or the regulatory authorities may wish to perform onsite audits. The Investigator will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested.

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor(s) will visit the Investigator(s) at regular intervals during the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contract(s) between the institution, Investigator, and Biogen.

18.5. Publications

Details are included in the clinical trial agreement for this study.

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

19.1.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of SAE reports. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or randomized, the IRT vendor will provide each study site with appropriate training, access rights, and a user manual.

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a web-based electronic data capture (EDC) tool developed by IQVIA and configured by the EDC vendor.

19.1.4. Central Laboratories for Laboratory Assessments

Biogen has selected a central laboratory service to perform all standard hematology, blood chemistry, and urinalysis testing for the study. This central laboratory will also receive, track, and ship all urine, blood, CSF samples, and DNA for specialized ApoE ε4 genotyping, PK, biomarker, and ADA testing, including aliquots from these samples retained as backup in case original samples are lost or not evaluable. Blood samples collected for future DNA testing will be processed to purify DNA and stored by the central laboratory.

Laboratories performing specialized testing will be identified in regulatory documentation. These laboratories will use appropriately validated or qualified assays to test study samples.

19.1.5. Central Facility for Other Assessments

A central imaging laboratory has been selected by Biogen to read and interpret all MRIs for this study within the timeframe specified in the procedural manual for MRI. In cases of ARIA-E and ARIA-H, the central imaging laboratory must expedite notification to the PI and the Sponsor. For the purposes of study conduct, the MRI interpretations from the central reader will prevail over those from the local radiologist.

The central imaging laboratory will also collect PET scans and assess the screening scan for eligibility criteria.

19.1.6. Neurocognitive Assessments

Biogen selected a rater management group to establish rater qualification, study-specific training, and oversight. The study raters are required to complete qualifications steps and required training prior to administering study assessments. The rater management group will oversee the assessments per project-specific plans.

19.2. Study Committees

19.2.1. Advisory Committee

An advisory committee will be formed to provide scientific and medical direction for the study and to oversee the administrative progress of the study. The advisory committee will meet periodically to monitor subject accrual and oversee study conduct, including advising on study design and execution. The advisory committee will be blinded to subject treatment assignments during the study.

Members of the advisory committee will include external experts in Alzheimer's disease. Biogen will designate one of the participating external experts to be the chairperson of the advisory committee.

19.2.2. Independent Data Monitoring Committee

The IDMC will be formed to review ongoing safety and tolerability data. Members of the IDMC will not be allowed to participate as Investigators in this study. The IDMC will review safety data on an ongoing basis to ensure safe and proper treatment of subjects. The IDMC, based on the nature, frequency, and/or severity of an AE(s) may recommend protocol modification(s), dose suspension, dose termination or study termination. An IDMC charter will provide full guidance on the function and practices to be followed by the IDMC.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the EC/IRB and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the EC/IRB before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, Biogen may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Sections 17.2 and 17.3).

19.4. Ethics Committee/Institutional Review Board Notification of Study Completion or Termination

Where required, the regulatory authorities and EC/IRBs must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator must notify Biogen of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

Biogen will designate one or more of the participating Study Investigators as a signatory for the study report. This determination will be made by several factors including but not limited to the Investigator's experience and reputation in the studied indication, the Investigator's contribution to the study in terms of design, management, and/or subject enrollment, or by other factors determined to be relevant by Biogen.

20. REFERENCES

Albert MS, DeKosky ST, Dickson D, 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(3):270-9.

Alzheimer's Disease International. World Alzheimer Report 2014: Dementia and risk reduction. London: Alzheimer's Disease International (ADI); 2014.

Chow S, Chang M. Adaptive Design Methods in Clinical Trials, Second Edition. Second Edition ed. Boca Raton, FL: Chapman and Hall/CRC; 2011.

Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol. 2010;9(11):1118-27.

Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 2014;13(6):614-29.

Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002;297(5580):353-6. Epub 2002 Jul 20.

Hock C, Konietzko U, Streffer JR, et al. Antibodies against beta-amyloid slow cognitive decline in Alzheimer's disease. Neuron. 2003;38(4):547-54. Epub 2003/05/27.

Jack CR, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013;12(2):207-216.

Koffie RM, Meyer-Luehmann M, Hashimoto T, et al. Oligomeric amyloid beta associates with postsynaptic densities and correlates with excitatory synapse loss near senile plaques. Proc Natl Acad Sci U S A. 2009;106(10):4012-7.

Kuchibhotla KV, Goldman ST, Lattarulo CR, et al. Abeta plaques lead to aberrant regulation of calcium homeostasis in vivo resulting in structural and functional disruption of neuronal networks. Neuron. 2008;59(2):214-25.

Kumar-Singh S, Pirici D, McGowan E, et al. Dense-core plaques in Tg2576 and PSAPP mouse models of Alzheimer's disease are centered on vessel walls. American Journal of Pathology. 2005;167(2):527-43. Epub 2005/07/29.

Lenderking WR, Steenrod A, Rüdell K, et al. Options for Evaluating Treatment Benefit in MCI and Prodromal Alzheimer's Disease: Content Validity of the Perceived Deficits Questionnaire (PDQ) in Patients with Early Symptoms of Cognitive Decline. Advances in Alzheimer's Disease. 2014;3:1-10. Epub March 2014.

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. Alzheimer's and Dementia. 2011;7(3):263-269.

Meyer-Luehmann M, Spires-Jones TL, Prada C, et al. Rapid appearance and local toxicity of amyloid-beta plaques in a mouse model of Alzheimer's disease. Nature. 2008;451(7179):720-4.

Morris JC, Blennow K, Froelich L, et al. Harmonized diagnostic criteria for Alzheimer's disease: recommendations. J Intern Med. 2014;275(3):204-13.

Ostrowitzki S, Deptula D, Thurfjell L, et al. Mechanism of amyloid removal in patients with Alzheimer disease treated with gantenerumab. Arch Neurol. 2012;69(2):198-207. Epub 2011 Oct 10.

Pfeifer M, Boncristiano S, Bondolfi L, et al. Cerebral hemorrhage after passive anti-Abeta immunotherapy. Science. 2002;298(5597):1379. Epub 2002/11/16.

Racke MM, Boone LI, Hepburn DL, et al. Exacerbation of cerebral amyloid angiopathy-associated microhemorrhage in amyloid precursor protein transgenic mice by immunotherapy is dependent on antibody recognition of deposited forms of amyloid beta. J Neurosci. 2005;25(3):629-36. Epub 2005/01/22.

Rozkalne A, Spires-Jones TL, Stern EA, et al. A single dose of passive immunotherapy has extended benefits on synapses and neurites in an Alzheimer's disease mouse model. Brain Res. 2009;1280:178-85.

Sperling RA, Jack Jr CR, Black SE, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: Recommendations from the Alzheimer's Association Research Roundtable Workgroup. Alzheimers Dement. 2011;7(4):367-385.

Spires-Jones TL, Mielke ML, Rozkalne A, et al. Passive immunotherapy rapidly increases structural plasticity in a mouse model of Alzheimer disease. Neurobiol Dis. 2009;33(2):213-20.

Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke. 2001;32(6):1318-22.

Weller RO, Subash M, Preston SD, et al. Perivascular drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and Alzheimer's disease. Brain Pathol. 2008;18(2):253-66.

Wilcock DM, Colton CA. Immunotherapy, vascular pathology, and microhemorrhages in transgenic mice. CNS Neurol Disord Drug Targets. 2009;8(1):50-64. Epub 2009/03/12.

Winkler DT, Bondolfi L, Herzig MC, et al. Spontaneous hemorrhagic stroke in a mouse model of cerebral amyloid angiopathy. J Neurosci. 2001;21(5):1619-27. Epub 2001/02/27.

21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease", and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

ENGAGE

221AD301

Statistical Analysis Plan

Placebo-Controlled Period

STATISTICAL ANALYSIS PLAN
Placebo-Controlled Period

Product Studied: Aducanumab
Protocol Number: 221AD301

A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease

Protocol Version: Version 6.0
Date of Protocol: 28 Jun 2018

Date of Statistical Analysis Plan: 11 Sep 2018, Final V1.0

Written By: PPD

12Sep2018
Date

12Sep 2018
Date

Approved By:

12 Sep 2018
Date

PPD

12 Sep 2018
Date

Table of Contents

List of Abbreviations

Aβ	β-amyloid
AD	Alzheimer's disease
ADAS-Cog 13	Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items)
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment version)
ADNI	Alzheimer's Disease Neuroimaging Initiative
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
ApoE ε4	apolipoprotein E4
ApoE ε4+	apolipoprotein E4 carrier
ApoE ε4-	apolipoprotein E4 non-carrier
ARIA	amyloid related imaging abnormalities
ARIA-E	amyloid related imaging abnormality-edema
ARIA-H	amyloid related imaging abnormality-hemorrhage or superficial siderosis
ASL-MRI	arterial spin labeling magnetic resonance imaging
AST	aspartate aminotransferase
BL	baseline
BLQ	below the limit of quantification
BMI	body mass index
bpm	beats per minute
BUN	blood urea nitrogen
CAM	Caregiver Assessment Measure
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CIR	copy increment from reference
C_{max}	observed maximum serum aducanumab concentration
C_{min}	observed minimum serum aducanumab concentration
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAT	Common Toxicity Criteria for Adverse Events
CV	coefficient of variation
EAIR	exposure-adjusted incidence rate
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D	EuroQol health status measure
EQ-5D (IR-I)	EuroQol health status measure, informant reported on informant's own health status
EQ-5D (IR-S)	EuroQol health status measure, informant reported on subject

EQ-5D (SR)	EuroQol health status measure, subject self-reported
FU	Follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl-transferase
HCP	health care professional
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IXRS	Interactive Voice/Web Response System
LDH	lactate dehydrogenase
LMCI	late mild cognitive impairment
LTE	long-term extension
LOCF	last observation carried forward
MCI	mild cognitive impairment
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-model repeated measures
MMSE	Mini-Mental State Examination
MOCA	Montreal Cognitive Assessment
mPDQ-20	Perceived Deficits Questionnaire-20 modified version
MRI	magnetic resonance imaging
NIA-AA	National Institute on Aging-Alzheimer's Association
NPI-10	Neuropsychiatric Inventory-10
PCS	potentially clinically significant
PET	positron emission tomography
pH	potential of hydrogen
PI	Principal Investigator
PK	pharmacokinetic(s)
PMM	pattern mixture model
PP	per-protocol
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
ROI	region of interest
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
SUVR	standard uptake value ratio
TEAE	treatment-emergent adverse event
tf-fMRI	task free functional MRI
ULN	upper limit of normal
US	United States
WHO	World Health Organization

1 DESCRIPTION OF OBJECTIVES AND ENDPOINTS

1.1 Primary Objective and Endpoint

The primary objective of this study is to evaluate the efficacy of monthly doses of aducanumab in slowing cognitive and functional impairment as measured by changes in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score as compared with placebo in subjects with early Alzheimer's Disease (AD).

The primary endpoint that relates to this objective is change from baseline in CDR-SB score at Week 78.

1.2 Secondary Objectives and Endpoints

The secondary objectives of this study are:

- To assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by the Mini-Mental State Examination (MMSE).
- To assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by Alzheimer's Disease Assessment Scale-Cognitive Subscales (13 items) [ADAS-Cog 13].
- To assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI].

The secondary endpoints are:

- Change from baseline in MMSE score at Week 78.
- Change from baseline in ADAS-Cog 13 score at Week 78.
- Change from baseline in ADCS-ADL-MCI score at Week 78.

1.3 Tertiary Objectives and Endpoints

1.3.1 Tertiary Objectives

Safety and Tolerability

- To assess the safety and tolerability of monthly doses of aducanumab.
- To assess the immunogenicity of aducanumab.

Biomarker/Efficacy/Quality of Life

- To assess the effect of aducanumab on cerebral amyloid plaque content as measured by amyloid positron emission tomography (PET) imaging (in a subset of approximately 400 subjects).
- To assess the effect of aducanumab on behavior as measured by the Neuropsychiatric Inventory-10 (NPI-10).
- To assess the effect of aducanumab on subject health status, measured by EuroQol health status measures (EQ-5D [informant-rated and subject self-reported]).
- To assess the effect of aducanumab on subject self-reported cognitive function, measured by the modified Perceived Deficits Questionnaire-20 (mPDQ-20).
- To assess the correlation between primary endpoint and cerebral amyloid plaque content as measured by PET imaging.

Pharmacokinetics

- To collect and characterize the pharmacokinetic (PK) parameters of aducanumab in serum

1.3.2 Tertiary Endpoints

Safety and Tolerability

- Incidence of all adverse events (AEs) and serious adverse events (SAEs).
- Brain magnetic resonance imaging (MRI) findings including incidence of amyloid related imaging abnormality-edema (ARIA-E) and amyloid related imaging abnormality-hemorrhage or superficial siderosis (ARIA-H).
- Clinical laboratory shifts in reported values.
- Clinically significant changes in vital sign measurements and electrocardiograms (ECGs).
- Incidence of anti-aducanumab antibodies in serum.

Biomarkers/Efficacy/Quality of Life

- Change from baseline in amyloid PET signal at Week 26 (in a subset of sites and subjects).
- Change from baseline in amyloid PET signal at Week 78 (in a subset of sites and subjects).
- Change from baseline in NPI-10 score at Week 78.
- Change from baseline in subject-self-reported EQ-5D index score at Week 78.
- Change from baseline in informant-rated subject EQ-5D index score at Week 78.
- Change from baseline in mPDQ-20 at Week 78.
- Correlation between the primary endpoint and cerebral amyloid plaque content as measured by PET imaging over time.

Pharmacokinetics:

- Serum concentrations and PK parameters of aducanumab.

1.4 Additional Exploratory Objectives and Endpoints

1.4.1 Additional Exploratory Objectives

Biomarker

- To assess the effect of aducanumab on various morphometric measures in certain brain areas as measured by MRI.
- To assess the effect of aducanumab on functional connectivity by task free functional MRI (tf-fMRI) (where available, in a subset of sites and subjects).
- To assess the effect of aducanumab on cerebral blood flow by arterial spin labeling (ASL)-MRI (where available, in a subset of sites and subjects).
- To assess the effect of aducanumab on disease- or treatment-related biomarkers in cerebrospinal fluid (CSF), which may include, but are not limited to, amyloid and tau proteins (in a subset of subjects).
- To assess the effect of aducanumab on disease- or treatment-related biomarkers in blood, which may include, but are not limited to, amyloid and tau proteins.
- To assess the effect of aducanumab on tau pathology by tau PET imaging (where available, in a subset of sites and subjects).

Health Outcomes

- To assess the effect of aducanumab on the informant/care partner's own health status, measured by the EQ-5D.
- To assess the effect of aducanumab on caregiver burden as measured by the Caregiver Assessment Measure (CAM).

1.4.2 Additional Exploratory Endpoints

Biomarkers

- Change from baseline in whole brain volume, hippocampal volume, ventricular volume, and cortical gray matter volume measured by MRI over time.
- Change from baseline in functional connectivity as measured by tf-fMRI over time (where available, in a subset of sites and subjects).
- Change from baseline in cerebral blood flow as measured by ASL-MRI over time (where available, in a subset of sites and subjects).
- Change from baseline in CSF biomarkers, which may include, but are not limited to, amyloid or tau proteins at Week 78 (in a subset of subjects).
- Change from baseline over time in blood biomarkers, which may include, but are not limited to, amyloid or tau proteins.
- Change from baseline in tau PET signal at Week 78 (where available, in a subset of sites and subjects).

Health Outcomes

- Change from baseline in informant/care partner's own EQ-5D index-score at Week 78.
- Changes on the CAM over time.

2 STUDY DESIGN

2.1 Study Overview

Study 221AD301 (ENGAGE) is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects with early AD, including mild cognitive impairment (MCI) due to AD and a subset of mild AD, followed by an optional dose-blinded long-term extension (LTE) period of up to 5 years. Approximately 1605 subjects will be enrolled across approximately 150 centers globally. The primary study objective is to evaluate the efficacy of monthly doses of aducanumab on the CDR-SB relative to placebo. Secondary objectives include assessment of the effect of monthly doses of aducanumab on clinical progression as compared to placebo. The safety of monthly doses of aducanumab will also be evaluated.

Table 1: Dosing Scheme for Aducanumab by Treatment Group and ApoE ε4 Carrier Status: Placebo-Controlled Period

Dose (every 4 weeks)		**1**	**2**	**3**	**4**	**5**	**6**	**7 to 20**
Treatment Group	**Treatment Group Stratified by ApoE Status[2]**	**Dose (mg/kg)**						
High Dose	**High Dose - ApoE ε4 (+)**	1	1	3	3	6	6	10[1]
	High Dose - ApoE ε4 (-)	1	1	3	3	6	6	10
Low Dose	**Low Dose - ApoE ε4 (+)**	1	1	3	3	3	3	3
	Low Dose - ApoE ε4 (-)	1	1	3	3	3	3	6
Placebo	**Placebo - ApoE ε4 (+)**	saline						
	Placebo - ApoE ε4 (-)	saline						

[1] 10 mg/kg is the target dose for all ApoE ε4 carriers assigned to the aducanumab high-dose group. Subjects enrolled under protocol versions 1-3 and assigned to the previous high-dose of 6 mg/kg will be titrated to 10 mg/kg upon receipt of at least 2 doses at 6 mg/kg.

[2] ApoE ε4 status recorded in the Interactive Voice/Web Response System (IXRS).

Subjects will be randomized in a 1:1:1 ratio to 1 of the 3 treatment groups: aducanumab high dose, aducanumab low dose and placebo, with stratification based upon their apolipoprotein E4 (ApoE ε4) carrier status (carrier/non-carrier) and site. During the placebo-controlled period, subjects will receive infusions of aducanumab or placebo approximately every 4 weeks for approximately 18 months (a total of 20 doses). Dose levels may be different in the same treatment group based upon subjects' ApoE ε4 carrier status, and specifically, ApoE ε4

carriers will receive placebo, aducanumab 3 mg/kg, or aducanumab 10 mg/kg whereas ApoE ε4 non-carriers will receive placebo, aducanumab 6 mg/kg, or aducanumab 10 mg/kg. Aducanumab will be titrated for up to 6 doses prior to reaching the target dose as shown in Table 1 and Figure 1. Note: As of Protocol Version 4, 10 mg/kg is the target dose for all ApoE ε4 carriers in the high-dose group. ApoE ε4 carriers who were randomized to the high dose group when the target dose was 6 mg/kg (under protocol versions prior to Version 4) must have received 2 or more doses at 6 mg/kg prior to being titrated up to 10 mg/kg.

At the end of the double-blind, placebo-controlled treatment period, subjects who meet the extension entry criteria may enter a long-term safety and efficacy extension period, with all subjects receiving aducanumab approximately every 4 weeks (up to a total of 65 doses over 5 years). The treatment group for the LTE period will be assigned at the same time as the randomization for the placebo-controlled period, regardless of whether a subject entering the LTE period or not. Subjects who are assigned to the placebo group during the placebo-controlled period will be assigned to 1 of 2 active treatment groups in a 1:1 ratio (aducanumab low dose: aducanumab high dose) and randomization will be stratified by their ApoE ε4 carrier status; for those who enter the LTE period, aducanumab will be titrated for up to 6 doses prior to reaching the target dose following the same schedule described for the placebo-controlled period. Subjects who are assigned to either aducanumab low dose or aducanumab high dose group in the placebo-controlled period will continue in the same treatment group for the LTE period; those who enter the LTE period will maintain the dosing scheme outlined in the protocol at the time of transition from the placebo-controlled period to the LTE period (e.g. subjects who are on stable dosing in the placebo-controlled period will continue on the same dose, subjects who are on a titration regimen during the transition will continue to titrate into the LTE period, and ApoE ε4 carrier subjects who are enrolled in the LTE and randomized to the high-dose group prior to implementation of version 4 of the protocol will be allowed to titrate to 10 mg/kg).

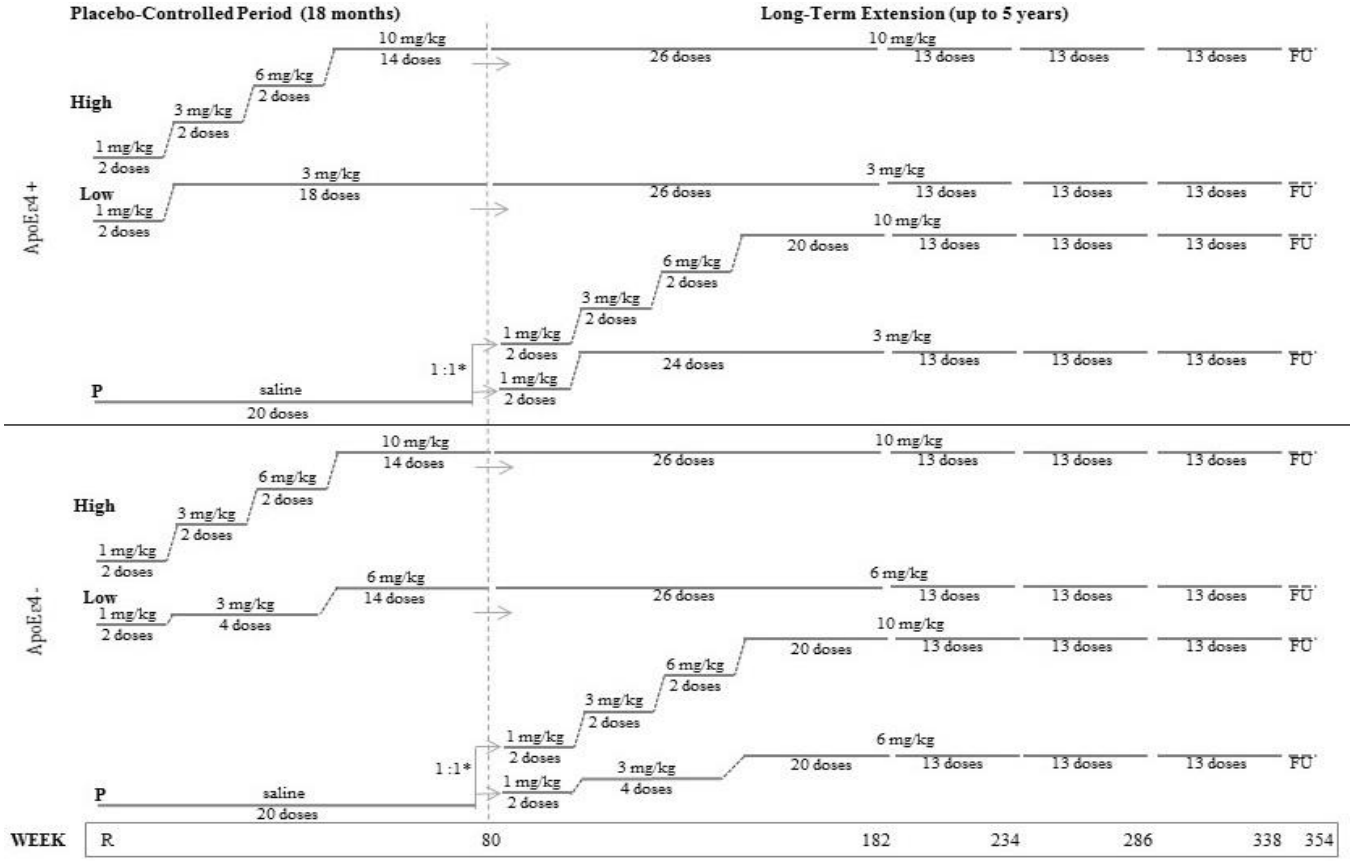
Individual dose adjustments may be implemented in subjects who develop amyloid related imaging abnormalities (ARIA). See Protocol Section 7.2.1.

The total duration of study participation for each subject only participating in the placebo-controlled period of the study will be up to approximately 102 weeks, including a series of Screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, and a safety follow-up (FU) period of approximately 18 weeks after the final dose. The total duration of study participation for each subject participating in the placebo-controlled period and the LTE period will vary and be up to approximately 362 weeks, including a series of Screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, a 4-week FU period, a 256-week aducanumab dose-blind treatment period, and a safety FU period of approximately 18 weeks after the final dose.

Investigators, study site staff (except for the designated unblinded pharmacist/technician), and study subjects will be blinded to the subjects' randomized treatment assignment for the placebo-controlled period. During the LTE period, investigators and subjects will remain blinded to the treatment assignment in the placebo-controlled period and the aducanumab dose for the LTE period.

2.2 Study Schematic

Figure 1: Study Design



ApoE ε4 +/- = apolipoprotein E4 positive/negative; FU = follow-up; P = placebo; R = randomization date.
*Subjects who are assigned to placebo during the placebo-controlled period are randomized in a 1:1 ratio to high and low dose aducanumab treatment (stratified by their ApoE ε4 carrier status) for the long-term extension period on Study Day 1.

2.3 Schedule of Events

See Protocol Section 4.2.

3 SAMPLE SIZE JUSTIFICATION

The study's sample size is based, in part, on results from a protocol-specified interim analysis from Study 221AD103 which included 1 year data from 1, 3 and 10 mg/kg treatment groups.

A sample size of 450 subjects per treatment group (1350 in total) was planned to have approximately 90% power to detect a true mean difference of 0.5 in change from baseline CDR-SB at Week 78 between the 2 treatment groups. This power calculation was based on a 2-sided t-test assuming equal variance with a final significance level of 0.05, a standard deviation (SD) of 1.92 and a drop-out rate of 30%. The SD estimate of 1.92 for Week 78 reflected a 39% increase over the SD from the protocol-specified interim analysis of 1-year data.

The assumed true mean difference of 0.5 between the 2 treatment groups represents an approximately 25% reduction in the placebo mean change from baseline at Week 78 if the placebo mean change is estimated to be 2.

As defined in the protocol, the sample size for this study (and for the identically designed Study 221AD302) was reassessed in a blinded manner in November 2017 (approximately 3 months before enrollment completion and with about 10.6% of the data available on the primary endpoint from Studies 221AD301 and 221AD302 combined). At this timepoint, the SD of the primary endpoint was estimated based on the pooled blinded data from two studies using a modified version of Gould-Shih simple-adjustment one sample variance (Zucker et al. 1999):

$$s_{adj}^2 = s_{os}^2 - \frac{2N}{9(N-1)}\delta^2,$$

where N denotes the number of subjects included in the analysis for blinded sample size re-estimation (subjects with both baseline and Week 78 CDR-SB available at the time of sample size re-estimation), δ is the assumed true treatment effect (same treatment effect assumed for both the high dose group and low dose group in this analysis), and s_{os}^2 is the unadjusted one sample variance of the primary endpoint estimate from the pooled blinded data.

As a result of this analysis, the sample size has been increased from 1350 to 1605 (450 to 535 per treatment group) to assure adequate power for detecting a mean treatment effect of 0.5.

4 STATISTICAL ANALYSIS METHODS

4.1 General Considerations

This statistical analysis plan (SAP) only covers the analyses for the primary, secondary and tertiary objectives for the placebo-controlled portion of the study. Hereafter, the placebo-controlled portion of the study will be referred to as "the study" in the rest of this SAP (e.g.,

completion of the study means completion of the placebo-controlled portion). A separate SAP will be prepared for the analyses of the LTE period and integrated analyses across both portions of the study. The analyses of additional exploratory endpoints will be documented separately.

Summary tables will be presented using descriptive summary statistics. For continuous variables, summary statistics will generally include: number of subjects with data, mean, standard deviation, median, 25% percentile, 75% percentile, minimum and maximum. For categorical variables, this will generally include: number of subjects randomized or dosed, number with data, and the percent of those with data in each category.

There are two types of analysis displays for tables: by treatment group (analysis display A in Appendix 6.1) and by treatment group stratified by ApoE status (analysis display B in Appendix 6.1; here ApoE status refers to the status recorded in IXRS [see Table 1 for correspondence between treatment groups and treatment groups stratified by ApoE status]). The analysis display for each analysis will be defined in each section. All the listings will be presented by treatment group stratified by ApoE status, unless otherwise specified.

Unless otherwise specified, baseline value is defined as the most recent non-missing measurement collected prior to the first dose. Change from baseline will be defined as post-baseline value minus baseline value.

Unless stated otherwise, all statistical tests will be 2-sided with statistical significance level of 0.05.

The statistical software, SAS® will be used for all summaries and analyses.

4.1.1 Analysis Population

- Intent-to-treat (ITT) population:
  The Intent-to-treat population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo).

- Per-protocol (PP) population:
  The per-protocol population is defined as all subjects in the ITT population and also
  - had no violations of the following inclusion criteria:
    - Must have at least 6 years of education or work experience to exclude mental deficits other than MCI or mild AD;
    - Must have a positive amyloid PET scan;
    - Must have:
      - A CDR-Global Score of 0.5;
      - A Repeatable Battery for Assessment of Neuropsychological Status (RBANS) score of 85 or lower indicative of objective cognitive impairment (based upon the Delayed Memory Index score);
      - An MMSE score between 24 and 30 (inclusive).
  - had at least 14 infusions.
  - did not make any change to concomitant AD symptomatic medications during the study.

- ^{18}F-florbetapir amyloid PET analysis population:
  The ^{18}F-florbetapir amyloid PET analysis population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo), used ^{18}F-florbetapir ligand for amyloid PET scan, and had an evaluable baseline amyloid PET SUVR value for the composite region-of-interest using cerebellum as the reference region.

- ^{18}F-flutemetamol amyloid PET analysis population (applicable only to Japan):
  The ^{18}F-flutemetamol amyloid PET analysis population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo), used ^{18}F-flutemetamol ligand for amyloid PET scan, and had an evaluable baseline amyloid PET SUVR value for the composite region-of-interest using cerebellum as the reference region.

- Safety population:
  The safety population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo). It is the same population as the ITT population.

- Safety MRI population:
  The safety MRI population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo) and had at least one post-baseline MRI assessment.

- PK analysis population:
  The PK analysis population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo) and had at least one measurable aducanumab concentration in serum.

- Immunogenicity population:
  The analysis population for immunogenicity is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo) and had at least one post-dose sample evaluable for immunogenicity.

4.2 Background Characteristics

The summaries in this section will be based on the ITT population. Unless otherwise specified, summary tables will be presented by treatment group (analysis display A in Appendix 6.1) and by treatment group stratified by ApoE status (analysis display B in Appendix 6.1; here ApoE status refers to the status recorded in IXRS [see Table 1 for correspondence between treatment groups and treatment groups stratified by ApoE status]). All the listings will be presented by treatment group stratified by ApoE status, unless otherwise specified.

4.2.1 Accounting of Subject

Disposition of subjects will be summarized and the summary data will include number (%) of subjects randomized and dosed, number (%) of subjects who completed the treatment/study, and number (%) of subjects who discontinued treatment and/or withdrew from study. For subjects who discontinued treatment and/or withdrew from study, the reasons for discontinuation and/or withdrawal, and days on treatment and days on study will be summarized and listed. The number of subjects discontinuing treatment prior to each scheduled clinical efficacy assessment will be summarized (presented by treatment group), i.e., the number of subjects discontinuing treatment between Day 1 and Week 26, the number of subjects discontinuing treatment between Week 26 and Week 50 visit, etc. A similar summary will be done for subjects who withdrew from study (presented by treatment group). Time to treatment discontinuation and time to study withdrawal will be displayed by Kaplan-Meier plot (presented by treatment group).

Number of subjects in each analysis population will be summarized. Number of subjects dosed will be summarized by region, country and site. In addition, number of subjects who completed the treatment/study will be summarized by region and country (presented by treatment group).

The categorization of region is based not only on consideration of geography but also on type of health care system and access to health care in each country. This region category will be used in all analysis, including the demographics, the covariate in statistical models and subgroup analysis. The categories for regions will be:

- Region 1: United States (US);
- Region 2: European countries (including Austria, Denmark, France, Germany, Italy, Portugal, Spain and United Kingdom), plus Australia and Canada;
- Region 3: Asia countries (including Japan, South Korea and Taiwan).

4.2.2 Demographics and Baseline Characteristics

The demographic data including age, gender, ethnicity, race, height, weight, and body mass index (BMI) will be summarized. Age will also be categorized and presented using the following two groupings: <50, 50-60, 61-70, 71-80, 81-85, >85 years, and ≤ 64, 65-74, ≥ 75.

Summary of the baseline characteristics of AD includes laboratory ApoE ε4 status (carrier or non-carrier), baseline clinical stage (MCI due to AD or mild AD), baseline clinical assessment including RBANS delayed memory index, CDR global score, CDR-SB, CDR cognitive subscore, CDR functional subscore, MMSE, ADAS-Cog 13, ADCS-ADL-MCI, number of years of formal education, number of years since first AD symptom, number of years since diagnosis of AD, AD treatment use that was stopped prior to entering the study (yes or no) and AD symptomatic medication use at baseline (yes or no; see Section 4.2.3 for definition of AD symptomatic medication use at baseline). ApoE ε4 carrier will be further classified as homozygote and heterozygote. MMSE will also be categorized by the following subgroups: <24, 24-26, 27-30. Subject listings will be generated for demographics and baseline characteristics.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number (%) of subjects with history (including both ongoing and not ongoing medical conditions) will be summarized by system organ class and preferred term. A listing of medical history will be generated.

Previous therapies for the treatment of AD stopped prior to entering the study, total duration of previous therapies and reason for stopping treatment will be summarized (presented by treatment group). A listing of previous therapies will also be generated.

4.2.3 Concomitant Medications and Non-Drug Therapies

All concomitant medications will be coded using the World Health Organization (WHO) medication dictionary. All concomitant non-drug therapies will be coded using the MedDRA dictionary. A concomitant medication/therapy will be defined as any therapy that was taken on or after the day of the first dose of study drug. This includes therapies that start prior to the initiation of the first dose if their use continues on or after the date of first dose. To define concomitant use for therapies with missing start or stop dates, the following additional criteria will be used:

- if both the start and stop dates of a therapy are missing, that therapy will be considered concomitant.
- if the start date of a therapy is missing and the stop date of that therapy fall on or after the date of the first dose, that therapy will be considered concomitant.
- if the start date of a therapy is prior to the date of the first dose and the stop date of that therapy is missing and the therapy is listed as continuing, that therapy will be considered concomitant, or
- if the start date of a therapy is prior to the date of the first dose and the stop date of that therapy is missing and the therapy is not listed as continuing, that therapy will be considered non-concomitant.

For a therapy with a partial start date, the year/month of the therapy date will be compared to that of the first dosing date to determine whether the therapy is concomitant.

The number (%) of subjects taking concomitant medication and non-drug therapies will be summarized. Non-drug therapies will be presented by treatment group. Concomitant medications and non-drug therapies will be listed.

AD symptomatic medications taken concomitantly at baseline are defined as AD symptomatic medications that were being taken at the time of the first dose, i.e., started prior to the first dose and continued until after the first dose. The number (%) of subjects taking AD symptomatic medications concomitantly at baseline will be summarized. In addition, number of subjects using Cholinesterase inhibitors only, Memantine only, or both at baseline will be summarized. Subjects who have any change in AD symptomatic medications after the initiation of study treatment will be summarized by the timing of change, i.e., the number of subjects changing between Day 1 and Week 26, the number of subjects changing between Week 26 and Week 50, etc. The summary for AD symptomatic medication use during study

will be presented by treatment group. The start and stop date of AD symptomatic medication will be listed for these subjects.

4.2.4 Protocol Deviations

Protocol deviations identified during site monitoring will be captured in a Protocol Deviation log and categorized as major or minor deviations based on Protocol Deviation Classification (see Appendix 6.2). The major protocol deviations will be summarized (presented by treatment group). Listings will be generated for the major and minor protocol deviations, respectively. A listing will be generated for subjects with incorrect stratification ApoE status, i.e., treatment stratification ApoE ε4 status in IXRS different from the laboratory ApoE ε4 status.

4.2.5 Study Drug Exposure and Study Drug Compliance

A summary table of study drug exposure and compliance will be provided. Number of infusions (aducanumab or placebo) received will be summarized as a categorical variable (categories as integers from 1 to 20, and 1-5, 6-10, 11-15, and 15-20) as well as a continuous variable. Number of weeks on study treatment (aducanumab or placebo), calculated as (date of last dose – date of first dose + 29)/7, will be summarized as a categorical variable (every 8 weeks from 0 to >= 72 weeks) as well as a continuous variable. Percentage of study treatment taken up to the last dose, calculated as (the actual number of infusions / by the number of infusions a subject is expected to take until the date of last infusion)*100, will be summarized as a continuous variable. This table will be presented by treatment group.

Due to the use of titration regimen in the study and possible dose reduction due to ARIA, another summary table will be provided including the following information: number of total infusions (categories of 1-5, 6-10, 11-15, and 15-20) as well as a continuous variable, number of infusions at each dose level (1 mg/kg, 3 mg/kg, 6 mg/kg and 10 mg/kg, respectively) summarized as a categorical variable as well as a continuous variable, number of subjects with dose increase (placebo to 1 mg/kg, 1 to 3 mg/kg, 3 to 6 mg/kg and 6 to 10 mg/kg, respectively), number of subjects with dose reduction (1 mg/kg to placebo, 3 to 1 mg/kg, 6 to 3 mg/kg and 10 to 6 mg/kg, respectively), maximum dose level received, and cumulative dose (as a continuous variable). This table will be presented by treatment group stratified by ApoE status.

A listing of study drug administration records, including dose level at each infusion, cumulative number of infusions and cumulative dose will be provided. A listing of aducanumab lot numbers will be provided.

A listing of study drug administration records for placebo subjects who received any doses of active treatment will be provided.

4.3 Efficacy Analysis

4.3.1 General Considerations

For efficacy endpoints, the following treatment groups of aducanumab (per randomization) will be evaluated and compared with placebo:

- Aducanumab high-dose (10 mg/kg in ApoE ε4 carriers [including 6 mg/kg for subjects enrolled under protocol versions 1-3 who do not have the opportunity to uptitrate to 10 mg/kg prior to completing Week 78 of the study] and 10 mg/kg in ApoE ε4 non-carriers).
- Aducanumab low-dose (3 mg/kg in ApoE ε4 carriers and 6 mg/kg in ApoE ε4 non-carriers).

All efficacy analyses will be performed on the ITT population. In addition, the primary and secondary endpoints will also be performed on the per-protocol population. The efficacy analysis will be presented by treatment group (per randomization), i.e., aducanumab high-dose, aducanumab low-dose and placebo (analysis display A in Appendix 6.1).

The primary, sensitivity and supplementary analyses for the primary and secondary endpoints are listed in Table 2.

Table 2. Analysis for Primary and Secondary Endpoints

Endpoint	Analysis	Analysis Population	SAP Section
CDR-SB	Primary: Analysis of change from baseline at Week 78 (MMRM)	ITT	4.3.2.1
	Sensitivity: Pattern mixture model (ANCOVA)	ITT	4.3.2.2.1
	Sensitivity: Copy increment from reference method (ANCOVA)	ITT	4.3.2.2.2
	Sensitivity: Imputation by natural disease progression (ANCOVA)	ITT	4.3.2.2.3
	Sensitivity: Tipping point analysis (ANCOVA)	ITT	4.3.2.2.4
	Supplementary: Censoring after intercurrent events (MMRM)*	ITT	4.3.2.3.1
	Supplementary: Per-protocol analysis (MMRM)	Per-protocol	4.3.2.3.2
	Supplementary: Responder analysis (Logistic regression)	ITT	4.3.2.3.3
	Supplementary: Slope analysis (MMRM)	ITT	4.3.2.3.4
	Supplementary: Divergence effect analysis (MMRM)	ITT	4.3.2.3.5
MMSE,	Primary: Analysis of change from baseline at Week 78 (MMRM)	ITT	4.3.3.1, 4.3.3.2, 4.3.3.3

ADAS-Cog 13, ADCS-ADL-MCI	Sensitivity: Pattern mixture model (ANCOVA)	ITT	4.3.3.4
	Supplementary: Censoring after intercurrent events (MMRM)*	ITT	4.3.3.4
	Supplementary: Per-protocol analysis (MMRM)	Per-protocol	4.3.3.4
	Supplementary: Slope analysis (MMRM)	ITT	4.3.3.4
	Supplementary: Divergence effect analysis (MMRM)	ITT	4.3.3.4

* Analysis excludes data collected after the following intercurrent events: (1) premature discontinuation of the study treatment and (2) any change to concomitant AD symptomatic medications during the study. All other analyses will include data collected after intercurrent events [ICH E9 (R1) Addendum 2017].

Visit windows for mapping efficacy endpoint

For efficacy data that are summarized or analyzed by visit, data collected on all scheduled visits and all unscheduled visits will be mapped to an appropriate analysis visit using the windowing scheme shown in Table 3. If there are 2 or more assessments available in the same analysis window for a subject, the assessment that is closest to the target visit day will be used for analysis. If there are 2 or more assessments in the same analysis window with the same distance from the target visit day, the later assessment will be used.

Table 3. Visit Windows for Efficacy Endpoints

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 26	183	[92, 266]
Week 50	351	[267, 448]
Week 78	547	[449, the end day of the placebo-controlled period *]
* The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter LTE, and is the last day in study for subjects who do not enter LTE.		

Handling of missing items for scales

If any of the individual items for the primary and secondary endpoints is missing, the total score of the corresponding endpoint will be imputed by prorating the observed scores [van Ginkel 2010].

For ADAS-Cog13, if 3 or fewer of 13 items (<25%) are missing, the total score will be imputed by the following algorithm: Total score = total score from the completed items * [maximum total score (=85) / maximum total score for the completed items]. The imputed number will be rounded up to the nearest integer. If more than 3 items are missing, the total score of ADAS-Cog 13 at that visit will be considered missing.

For ADCS-ADL-MCI, if 4 or fewer of 18 items (<25%) are missing, the total score will be imputed by a similar algorithm as that for ADAS-Cog 13. The imputed number will be

rounded up to the nearest integer. If more than 4 items are missing, the total score for ADCS-ADL-MCI at that visit will be considered missing.

The same imputation algorithm will be applied to CDR-SB and MMSE, if only 1 box (of 6) of CDR is missing or if only 2 or fewer items (out of 11) are missing for MMSE. If the score from more than 1 box of CDR or more than 2 items of MMSE is not available, the CDR-SB or MMSE at that visit will be considered missing.

The total score of the tertiary endpoint NPI-10 will be imputed using the same prorating principle if only 1 item (out of 10) is missing. For EQ-5D and mPDQ-20, if any item is missing, any total or sum involving that item will be considered missing.

Considerations for multiple comparison adjustments

A sequential (closed) testing procedure will be used to control the overall Type I error rate due to multiple comparisons for the primary endpoint. The order of treatment comparisons is as follows: aducanumab high-dose versus placebo and aducanumab low-dose versus placebo. All comparisons after the initial comparison with $p > 0.05$ will not be considered statistically significant.

Secondary endpoints have been rank prioritized, in the order shown in Section 1.2. In order to control for a Type I error for the secondary endpoints, a sequential closed testing procedure will be used and will include both the order of the secondary endpoints and treatment comparisons. Specifically, for each of the secondary endpoints, a sequential (closed) testing procedure, as for the primary endpoint, will be used to control the overall Type I error rate due to multiple treatment comparisons. If statistical significance is not achieved for 1 or 2 treatment comparisons, all endpoint(s) of a lower rank will not be considered statistically significant for that 1or 2 treatment comparisons, respectively.

There will be no multiple comparison adjustments for the sensitivity and supplementary analyses for the primary and secondary efficacy endpoints, the tertiary efficacy endpoints, the subgroup analyses or the additional analyses.

4.3.2 Primary Efficacy Endpoint

4.3.2.1 Primary analysis

The estimand of the primary analysis is the mean difference of the change from baseline CDR-SB scores at Week 78 between treatment groups in the ITT population [ICH E9 (R1) Addendum 2014, 2017]. All observed data will be included in the primary analysis, including data collected after intercurrent events [ICH E9 (R1) Addendum 2017], i.e., treatment discontinuation or a change in concomitant use of AD symptomatic medication.

The change from baseline CDR-SB scores will be summarized by treatment group at each post-baseline visit. A mixed model repeated measures (MMRM) model will be used as the primary analysis to analyze change from baseline CDR-SB using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline CDR-SB, baseline CDR-SB by time interaction, baseline MMSE, AD symptomatic medication use at baseline (yes/no; see Section 4.2.3 for definition of AD symptomatic medication use at baseline),

region, and laboratory ApoE ε4 status (carrier/non-carrier). An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive covariance structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. In the primary analysis, missing data are assumed to be missing at random [Rubin 1976].

4.3.2.2 Sensitivity analysis

The following sensitivity analyses will be performed to assess the robustness of the primary analysis to deviation from the missing-at-random assumption. All the sensitivity analyses will be conducted for the ITT population.

4.3.2.2.1 Pattern mixture model

The pattern mixture model (PMM) represents a general and flexible framework to model the predictive distribution of missing data conditional on the observed data [Little 1993, 1994]. It allows formulating assumptions regarding missing data in a transparent and clinically interpretable manner.

In the PMM framework, subjects are grouped into missing patterns so that subjects in the same pattern share similar missingness characteristics. In this analysis, missing patterns will be defined according to the reasons for early withdrawal from study as reported on the electronic case report form (eCRF). The following two patterns will be considered:

- Subjects who withdraw due to reasons that may be related to efficacy, including consent withdrawn, withdrawal by parent/guardian, investigator decision, loss of capacity, change of treatment, and disease progression;
- Subjects who withdraw due to reasons that are unlikely related to efficacy, including adverse event, lost to follow-up, death, pregnancy, relocation, protocol amendment, site terminated by sponsor/investigator, study visit burden, and other.

Subjects who withdraw due to reasons that may be related to efficacy will be penalized and their missing data will be imputed using the copy increment from reference (CIR) method [Carpenter et al. 2013] (see Section 4.3.2.2.2 for description of the CIR method). Subjects who withdraw due to reasons that are unlikely related to efficacy will be handled using the missing-at-random assumption and their missing data will be imputed using the standard multiple imputation method [Rubin 1987]. Subjects with missing data due to reasons other than early withdrawal (such as item missing, out of window, etc.) will be handled using the missing-at-random assumption. For both imputation methods, the following covariates will be included in the imputation model: treatment group, baseline CDR-SB, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). Implementation details can be found in Appendix 6.3.2.

The imputed datasets will be analyzed by an analysis of covariance (ANCOVA) model adjusting treatment group, baseline CDR-SB, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). The analyzed results from the imputed datasets will be combined based on Rubin's rules [Rubin

1987] assuming that the statistics estimated from each imputed dataset are normally distributed.

If intermediate missing values are encountered (such as data missing at Week 26 but are available at subsequent visits), a Markov chain Monte Carlo (MCMC) method that assumes multivariate normality will be used to impute the intermediate missing values and produce a monotone missing pattern (data with only terminal missing and no intermediate missing) [Li 1988; Schafer 1997].

4.3.2.2.2 Copy increment from reference method

The copy increment from reference (CIR) method will be applied to impute the post-withdrawal data for any aducanumab-treated subject who withdraws from study early based on data from the placebo group rather than the subject's own randomized treatment group [Carpenter et al. 2013]. Specifically, for a subject on aducanumab high dose (or aducanumab low dose) who withdraws early, his or her mean trajectory after early withdrawal is assumed to be parallel to the mean trajectory of the placebo group, and the difference between the two means is the same as the difference at the time of withdrawal. This method assumes that any benefit gained from previous treatment will be retained, but subjects progress as if they were on placebo after withdrawal from study. For any subject on placebo who withdraws early, his or her post-withdrawal profile will be imputed following the missing-at-random principle. Implementation details can be found in Appendix 6.3.1.

After all missing data have been imputed, an ANCOVA model adjusting treatment group, baseline CDR-SB, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier) will be applied to analyze the change from baseline CDR-SB.

4.3.2.2.3 Imputation by natural disease progression

Subjects are assumed to exhibit an evolution of the disease similar as the natural disease progression after early withdrawal from study (for all treatment groups). The natural disease progression is determined based on a snapshot of the Alzheimer's Disease Neuroimaging Initiative (ADNI) database [Mueller et al. 2005] obtained in May 2017. A subpopulation was defined that satisfies the major inclusion criteria of Study 221AD301 (and the identically designed Study 221AD302). In this subpopulation, the mean change from baseline CDR-SB at Week 78 is estimated to be about 1.52 for subjects with late mild cognitive impairment (LMCI) and about 2.06 for subjects with mild AD. The missing data at Week 78 for this study will be imputed using the linear extrapolation approach based on subjects' baseline clinical stage (MCI due to AD or mild AD). For example, assuming a mild AD patient whose last non-missing change from baseline CDR-SB measurement is 0.5 at Week 26, the change from baseline CDR-SB at Week 78 for this patient will be imputed as 0.5+2.06*(78-26)/78, which is 1.87. A similar algorithm will be applied to the MCI patients. After imputation, the change from baseline CDR-SB at Week 78 will be analyzed by an ANCOVA model adjusting treatment group, baseline CDR-SB, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier).

4.3.2.2.4 Tipping point analysis

The tipping-point analysis is a progressive stress-testing to assess how severe departures from missing-at-random must be in order to overturn the conclusion of the primary analysis [Yan et al. 2009]. For our study, subjects are assumed to have worse scores after early withdrawal from study compared to subjects who remain on study.

The missing data are first imputed by the standard multiple imputation (assuming missing at random). To reflect the worse performance after early withdrawal, pre-specified shift parameters δ_c and δ_t are added to the imputed values for subjects on placebo and aducanumab (include both low dose and high dose), respectively. The adjusted multiple imputed datasets will then be analyzed by an ANCOVA model and the results will be combined using the Rubin's rule for inference.

A range of shift parameters δ_c and δ_t will be applied and p-value will be calculated for each combination of δ_c and δ_t. The tipping region is defined as the combinations of δ_c and δ_t such that the treatment effect is no longer significant (p-value greater than the significance level).

The scientific plausibility of the tipping region will be evaluated. If implausible departures from the missing-at-random assumption (large δ) are needed in order to change the results from statistically significant to insignificant, the results of the primary analysis are considered to be robust to departure from the missing-at-random assumption.

4.3.2.3 Supplementary analysis

4.3.2.3.1 Censoring after intercurrent events

The primary analysis (Section 4.3.2.1) will be repeated with the data censored after any of the following intercurrent events (if multiple events occur to the same subject, data after the earliest event will be censored):

- premature discontinuation of the study treatment;
- any change to concomitant AD symptomatic medications during the study.

The estimate of this analysis reflects the treatment effect of aducanumab if the drug is taken as directed.

4.3.2.3.2 Per-protocol analysis

The per-protocol analysis will be done using the same model as the primary analysis (Section 4.3.2.1) and applying in the per-protocol population (Section 4.1.1).

4.3.2.3.3 Responder analysis

To further assess whether subjects on aducanumab progress differently from those on placebo, responder analysis will be conducted. The responders will be determined by a threshold of the primary endpoint, i.e., subjects whose change from baseline CDR-SB at Week 78 is smaller than or equal to the threshold will be classified as responders and otherwise will be classified as non-responders. All subjects with missing data at Week 78 will be classified as non-responders.

The responder analysis will be conducted for two threshold values: 0.5 or 1.5, i.e., subjects whose change from baseline CDR-SB at Week 78 ≤ 0.5 or ≤ 1.5. The number of responders

and the response rate will be summarized by treatment group. The dichotomized response, responder vs. non-responder, will be modeled using a logistic regression with the following covariates: treatment group, baseline CDR-SB, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratoy ApoE ε4 status (carrier/non-carrier). In addition to the two selected threshold values, the continuous responder curve that displays the percentage of responders under a wide range of threshold values will be presented by treatment group.

Since all missing data will be considered as non-response, which is a special form of missing-not-at-random, this analysis can provide additional insights for the robustness of the primary analysis results.

4.3.2.3.4 Slope analysis

Slope analysis will be conducted to assess the difference between each aducanumab treatment group and placebo in the slope of change from baseline in CDR-SB up to Week 78. A reduction in the slope of the aducanumab treatment group compared with placebo would indicate a slower rate of disease progression, thus reflecting a disease modifying effect of aducanumab. An MMRM model will be used, with dependent variable as the change from baseline CDR-SB score at each visit and with fixed effects of treatment group, time (as a continuous variable), treatment group-by-time interaction, baseline CDR-SB, baseline CDR-SB by time, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). The continuous time variable is calculated as number of years since the 1st infusion, so the slope estimate reflects the annual rate of change. The same methods as in the primary analysis will be considered for the covariance structure and the degrees of freedom.

4.3.2.3.5 Divergence effect analysis

A divergence effect analysis will be performed to assess whether the treatment difference between the aducanumab treated patients and the placebo patients increases over time [Li 2017]. A linear trend test will be conducted on treatment difference at Week 26, 50 and 78 estimated from the MMRM model of Section 4.3.2.1, to assess if the slope of the treatment difference is positive or not. Let the estimate of treatment difference be δ_i at time point t_i, where $t_i = 26$, 50 and 78 (week). The least-square estimate of the slope is

$$\beta_{DIF} = \frac{\sum(t_i - \bar{t})\delta_i}{\sum(t_i - \bar{t})^2},$$

where $\bar{t}$ is the mean of t_i's. The hypothesis to be tested is

$$H_0: \beta_{DIF} \leq 0 \quad \text{versus} \quad H_a: \beta_{DIF} > 0.$$

Given β_{DIF} is a linear combination of the treatment difference δ_i, this analysis can be implemented by the "estimate" statement in the SAS proc mixed procedure.

4.3.2.4 CDR subscores and CDR global score

The CDR is comprised of 6 domains: Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. CDR-SB is the sum of the scores

for these 6 domains. In addition, two CDR subscores have been proposed [Tractenberg 2005]: a "cognitive" subscore equaling the sum of the Memory, Orientation, and Judgment and Problem Solving box scores, and a "functional" subscore equaling the sum of Community Affairs, Home and Hobbies and Personal Care box scores. For each of the 6 box scores, and the CDR cognitive subscore and CDR functional subscore, the baseline value and the change from baseline at each post-baseline visit will be summarized by treatment group. The same MMRM model as the primary analysis will also be applied to the CDR cognitive subscore and CDR functional subscore.

The CDR global score is a composite score obtained by combining the 6 box scores using a scoring algorithm that weights memory as the primary domain and all other domains as secondary [Morris 1993]. The distribution of CDR global score will be summarized (as a categorical variable) by treatment group at each post-baseline visit.

4.3.3 Secondary Efficacy Endpoints

4.3.3.1 Primary analysis of MMSE

The change from baseline MMSE scores will be summarized by treatment group at each post-baseline visit. An MMRM model will be used as the primary analysis to analyze change from baseline MMSE using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline MMSE value, baseline MMSE by time interaction, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). The same methods as in the primary analysis will be considered for the covariance structure and the degrees of freedom.

4.3.3.2 Primary analysis of ADAS-Cog 13

The change from baseline ADAS-Cog 13 scores will be summarized by treatment group at each post-baseline visit. An MMRM model will be used as the primary analysis to analyze change from baseline ADAS-Cog 13 using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline ADAS-Cog 13, baseline ADAS-Cog 13 by time interaction, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). The same methods as in the primary analysis will be considered for the covariance structure and the degrees of freedom.

4.3.3.3 Primary analysis of ADCS-ADL-MCI

The change from baseline ADCS-ADL-MCI scores will be summarized by treatment group at each post-baseline visit. An MMRM model will be used as the primary analysis to analyze change from baseline ADCS-ADL-MCI using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline ADCS-ADL-MCI, baseline ADCS-ADL-MCI by time interaction, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). The same methods as in the primary analysis will be considered for the covariance structure and the degrees of freedom.

The primary analysis of ADCS-ADL-MCI will use the pooled data from both Studies 221AD301 and 221AD302 (analysis for each individual study will also be performed). Pooled data will be used for the primary analysis because functional outcomes are expected to be less sensitive to change within the study duration than cognition measures due to ceiling effects [Rockwood 2007], as subjects entering the study will have no or little measurable impairment at baseline. It has also been observed in previous studies of more impaired patients (mild to moderate/severe) that functional outcome treatment effect sizes are small [Hansen 2007].

4.3.3.4 Sensitivity/Supplementary analysis

The following sensitivity and supplementary analyses that are planned for the primary efficacy endpoint will also be conducted for the secondary efficacy endpoints:

- Pattern mixture model
- Censoring after intercurrent events
- Per-protocol analysis
- Slope analysis
- Divergence effect analysis

4.3.4 Tertiary Endpoints for Efficacy and Quality of Life

The baseline value and the change from baseline at each post-baseline visit for NPI-10 will be summarized by treatment group. An MMRM model will be used to analyze the change from baseline in NPI-10 using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline NPI-10, baseline NPI-10 by time interaction, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). Same methods as in the primary analysis will be considered for the covariance structure and the degrees of freedom.

For the following tertiary endpoints for patient-reported outcomes and quality of life, subject self-reported EQ-5D index score (SR), informant-rated subject EQ-5D index score (IR-S), and mPDQ-20, the baseline value and the change from baseline at each post-baseline visit will be summarized by treatment group. Additional analyses for these endpoints will be provided in a separate document.

4.3.5 Subgroup Analysis

Subgroup analyses will be performed for the primary endpoint (CDR-SB) and secondary endpoints (MMSE, ADAS-Cog13, ADAS-ADL-MCI). The following pre-defined subgroups will be considered:

- Laboratory ApoE ε4 status (carrier or non-carrier)
- Baseline clinical stage (MCI due to AD or mild AD) per the Investigator's assessment based on the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria
- Use of AD symptomatic medication at baseline (yes or no)

- Baseline MMSE (MMSE ≤ 26 or MMSE ≥ 27)
- Region (US, Europe/Canada/Australia, Asia; see Section 4.2.1 for definition of region)
- Age category (≤ 64, 65-74, ≥ 75)
- Gender (female or male)

A selective set of subgroup analyses will be performed for Amyloid PET data. Details will be defined in Sections 4.4.

4.4 Amyloid PET Analysis

4.4.1 Amyloid PET substudy

Every subject enrolled into the study must have a positive amyloid PET scan by visual read either at screening or obtained within 12 months of screening. Subjects enrolled into the amyloid PET substudy will have the quantitative standard uptake value ratio (SUVR) scores at screening and at each planned post-baseline visit. The amyloid PET substudy will include a subset of approximately 400 subjects in countries other than Japan where PET scans will be performed using ^{18}F-florbetapir ligand, and a small subset of subjects in Japan where either ^{18}F-florbetapir ligand or ^{18}F-flutemetamol ligand will be used. In the placebo-controlled period, amyloid PET assessments are scheduled at screening, Week 26, and Week 78.

4.4.2 Amyloid PET SUVR regions-of-interest and reference regions

Amyloid PET standardized uptake value ratio (SUVR) is a quantitative measure of cerebral amyloid plaque burden. The SUVR will be calculated for the following target brain regions-of-interest (ROIs): composite ROI, frontal cortex, parietal cortex, lateral temporal cortex, sensorimotor cortex, anterior cingulate cortex, posterior cingulate cortex, medial temporal cortex, occipital cortex, striatum, and statistical ROI normalized to reference region activity. Additionally, SUVR ROIs including pons and deep subcortical white matter which are believed to be least affected by amyloid pathology will also be evaluated. The composite ROI will comprise of major cortical regions part of the frontal, parietal, lateral temporal, sensorimotor, anterior, posterior cingulate and occipital cortices to serve as a summary measure of global cerebral amyloid burden. The statistical ROI is a region of interest consisting of the posterior cingulate cortex, precuneus and medial frontal cortex that has been demonstrated to yield optimal group separation between subjects with low and high amyloid burden across different reference regions. A negative change from baseline in composite ROI SUVR indicates a reduction in amyloid burden and a negative treatment difference (aducanumab minus placebo) favors aducanumab. The composite ROI will serve as the ROI of primary focus.

The following reference regions will be employed: cerebellum, cerebellum cropped, cerebellar white matter, cerebellar grey matter, deep subcortical white matter, pons, cerebellum + pons, cerebellar white matter + pons, deep subcortical white matter + cerebellum, deep subcortical white matter + pons and deep subcortical white matter + cerebellum + pons. Cerebellum will serve as the reference region of primary focus.

The composite ROI SUVR using cerebellum as the reference region will be used as the primary endpoint for amyloid PET analysis.

4.4.3 Amyloid PET analysis population

There are two amyloid PET analysis population: ^{18}F-florbetapir amyloid PET analysis population and ^{18}F-flutemetamol amyloid PET analysis population.

The following background characteristics tables will be generated for the ^{18}F-florbetapir amyloid PET analysis population and will be presented by treatment group: number of subjects enrolled by region and country, demography, baseline disease characteristics, medical history. The content of these tables will be the same as those described in section 4.2 for the ITT population, with the addition of baseline amyloid PET SUVR values summarized for the baseline characteristics of AD.

4.4.4 By visit summary and MMRM model

The baseline and change from baseline amyloid PET SUVR values will be summarized by treatment groups (placebo, low dose and high dose) and by visit for each of the target ROIs using cerebellum as the reference region for each of the amyloid PET analysis populations. In addition, the baseline and change from baseline amyloid composite ROI values will be summarized by treatment groups by visit for each of the reference regions for each of the amyloid PET analysis populations.

For the ^{18}F-florbetapir amyloid PET analysis population, an MMRM model will be used to analyze change from baseline SUVR for each target ROI with cerebellum as the reference region. Fixed effects of the model will include treatment groups (placebo, low dose and high dose), visit (Week 26 and Week 78), treatment group-by-visit interaction, baseline SUVR (continuous), baseline SUVR by visit interaction, baseline MMSE (continuous), laboratory ApoE ε4 status (carrier and non-carrier), and baseline age (continuous). Visit and treatment group will be treated as categorical variables in the model along with their interactions. An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence in any of the parameters, the heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive covariance structure will be used for all the parameters. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Adjusted means for each treatment group, pairwise adjusted differences with placebo, 95% confidence intervals for the differences and associated p-values will be presented at week 26 and week 78. The same MMRM model will also be used to analyze the change from baseline SUVR for the composite ROI with each of the reference regions. No multiple comparison adjustment will be used for amyloid PET analysis.

Subgroup analysis will be conducted on the ^{18}F-florbetapir amyloid PET analysis population using the same MMRM model for composite ROI using cerebellum as reference region for the following stratification factors: laboratory ApoE status (carrier or non-carrier, and this model will not use ApoE status as a covariate), baseline clinical stage (MCI due to AD or mild AD) and baseline composite ROI SUVR value in quartiles.

Visit windows for by visit analysis

For amyloid PET by visit summaries and MMRM models, the analysis visit should be defined using visit windows (see Table 4 below). The rationale is to use the same analysis visit windows as for the efficacy endpoints for Week 26 and Week 78. If there is more than 1 value in the same analysis visit window (>1 value for the same analysis visit) for a certain parameter for a subject, then the closest record to the target visit day will be used for the by visit analysis. If they are with the same distance from the target visit day, then the record with the later time will be used for the by visit analysis.

Table 4: Visit Windows for amyloid PET data

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 26	183	[92, 266]
Week 78	547	[449, the end day of the placebo-controlled period**]
* The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter in LTE, and is the last day in study for subjects who do not enter LTE.		

4.4.5 Correlation between amyloid PET and CDR sum of boxes

Pearson and Spearman correlation

Pearson and Spearman correlations between change from baseline amyloid PET composite ROI using cerebellum as reference region at Week 78 and change from baseline CDR-SB at Week 78 will be conducted by treatment groups (placebo, low dose and high dose, and active total) in the ^{18}F-florbetapir amyloid PET analysis population. Pearson and Spearman partial correlations adjusting for baseline amyloid PET composite ROI and baseline CDR-SB will also be conducted by treatment groups at Week 78. The estimated correlation coefficients, p-values and the 95% confidence intervals will be provided. Given that reductions in cerebral β-amyloid (Aβ) content may precede clinical effects (e.g., slowing of clinical decline), Pearson and Spearman correlations and partial correlations between change from baseline amyloid PET composite ROI at Week 26 and change from baseline CDR-SB at Week 78 will also be conducted.

Correlation analysis will be done on each individual study as well as in the pooled data of the 221AD301 and 221AD302 studies. The correlation analysis based on the pooled data will be considered as the primary analysis.

4.5 Safety Analysis

4.5.1 General Considerations

Analysis population

Safety population will be used for safety analyses of AEs, clinical laboratory data, Columbia Suicide Severity Rating Scale (C-SSRS) data, ECG data and vital sign data (all the safety data except for ARIA data). Safety MRI population will be used for analyses of ARIA data.

Safety treatment groups

Different from the randomization treatment groups, if a subject who was randomized to placebo group accidentally received one or more doses of the active treatment during the study, he/she will be classified as either low or high dose group for all the safety analyses, depending on the ApoE status and the maximal dose level of the active treatment received (Table 5). A listing of such subjects will be provided, as described in section 4.2.5. Safety treatment groups will be the same as the randomization treatment groups for other subjects (subjects randomized to active treatment groups, and subjects randomized to placebo without any accidental active dose). Safety treatment groups will be used for all the safety analyses unless otherwise specified.

Table 5: Safety treatment groups for placebo subjects with accidental active treatment

Randomization treatment group	Randomization ApoE status	Safety treatment group classification based on the maximum dose level of the accidental active treatment		
		>0 to 3 mg/kg	>3 to 6 mg/kg	>6 mg/kg
Placebo	ApoE ε4 (+)	Low dose	High dose	High dose
	ApoE ε4 (-)	Low dose	Low dose	High dose

Safety analysis displays

AEs, clinical laboratory data, C-SSRS data, ECG data and vital sign data (all the safety data except for ARIA data) will be summarized by treatment group (placebo, low dose, high dose and BIIB037 total; analysis display A in Appendix 6.1), unless otherwise specified. All the ARIA related tables will be presented by treatment group stratified by ApoE status (3 columns under each treatment group: ApoE ε4+, ApoE ε4- and total; analysis display B in Appendix 6.1), unless otherwise specified. A subset of AE tables will also be presented by treatment group stratified by ApoE status in addition to by treatment group. All the listings will be presented by treatment group stratified by ApoE status.

Incidence, incidence proportion and incidence rate

- Incidence and incidence proportion will be provided in incidence tables. Incidence is defined as the number of subjects who experienced an event. Incidence proportion is defined as the number of subjects who experienced an event divided by total number of subjects in the analysis population, i.e., percentage. Each subject will be counted only once within each category.

- Incidence and incidence rate will be provided in incidence rate tables. Two different kinds of incidence rate tables will be provided as appropriate for different analyses. Definitions are provided below.

  (1) Follow-up adjusted incidence rate – defined as the number of subjects who experienced an event divided by the total of entire follow-up time among the subjects in the analysis population. The entire follow-up time for a subject is defined as the time from the first dose until the last day on study. Each subject will be counted only once within each category.
  (2) Exposure-adjusted incidence rate (EAIR) – defined as the number of subjects who experience an event divided by the total exposure adjusted follow-up time among the subjects in the analysis population. The exposure adjusted follow-up time is defined as the time from the first dose until the initial occurrence of the event for those who experienced an event, or from the first dose until the end of follow-up (the last day on study) for those who did not. Each subject will be counted only once within each category.

4.5.2 Clinical Adverse Events

Treatment-emergent AEs (TEAEs)

All AEs will be analyzed based on the principle of treatment emergence. A treatment-emergent AE was defined as an AE that started or worsened after the start of first infusion of study treatment.

To define treatment emergence for AEs with missing start or stop date or time the following additional criteria will be used:

- if both the start and stop dates for a particular AE are missing, then that AE is considered treatment emergent;
- if the start date for a particular AE is missing and the stop date/time falls after the first dose date/time, then that AE is considered treatment emergent;
- if the start date for a particular AE was the same as the first dose date, and the start time was missing, then that event is considered treatment emergent.

For AEs with a partial start date, the year/month of the event date will be compared to that of the first dosing date to determine whether the event is treatment emergent.

In addition, SAEs that occurred since a subject was screened in the study and prior to the first infusion of study treatment, which by definition are not treatment-emergent, will be analyzed separately.

Only TEAEs will be included in the AE tables, unless otherwise specified. Listings of AEs will include all events, whether treatment-emergent or not.

As specified in the protocol, subjects were expected to return to the study site for an End of Study visit 18 weeks after the last administration of study treatment. However, some subjects may elect to continue study participation on a modified schedule after discontinuing treatment, possibly in substantial excess of 18 weeks. For most general AE summaries, AEs

with an onset more than 18 weeks after the last dose will be excluded (will specify in the footnote of the specific table). For incidence rate analyses excluding AEs more than 18 weeks after the last dose, the "last day on study" in follow-up time calculation will be replaced with "18 weeks after last dose or last day on study, whichever earlier". Summaries of deaths and AEs leading to study withdrawal, and other selected analyses will include all AEs regardless of the time since the last dose. Listings will include all AEs, unless otherwise specified.

4.5.2.1 Summary and incidence analysis

Overall summary of AE table will summarize the number of subjects with any AE, with any AE by maximum severity, the number of subjects with any related AE (related to study drug as assessed by investigator), the number of subjects with SAE, the number of subjects with related SAE, the number of subjects with AE leading to study drug discontinuation, the number of subjects with AE leading to study withdrawal, and the number of deaths. This table will be done by treatment group as well as by treatment group stratified by ApoE status.

The sorting order for AE incidence tables, unless otherwise specified, will be by decreasing frequency order of "BIIB037 total" column within each category in the tables presented by treatment group, and by decreasing frequency order of "BIIB037 high dose total" column within each category in the tables presented by treatment group stratified by ApoE status. A subject is counted only once within each category in each table. For example, for the table of AEs by system organ class and preferred terms sorted by decreasing frequency presented by treatment group, system organ class will be presented in decreasing frequency order of BIIB037 total column, and within each system organ class, preferred terms will be presented in decreasing frequency order of BIIB037 total column. A subject is counted only once within each system organ class and preferred term.

The following AE incidence tables will be provided (presented both by treatment group and by treatment group stratified by ApoE status, unless otherwise specified):

1. AEs by system organ class and preferred term sorted by decreasing frequency
2. AEs by system organ class and preferred term sorted by alphabetical order (by treatment group)
3. AEs by system organ class, high level group term and preferred term (by treatment group only)
4. AEs by system organ class (by treatment group)
5. AEs with at least 2% higher in incidence for either low or high dose compared to placebo by system organ class and preferred term
6. AEs by preferred term
7. AEs with an incidence of 5% or more in any treatment group by preferred term
8. Severe AEs by system organ class and preferred term (by treatment group)
9. Severe AEs by preferred term
10. AEs by maximum severity by system organ class and preferred term (by treatment group) (System organ class will be presented alphabetically. Preferred terms will be presented in decreasing frequency order. Maximum severity will be presented within each preferred term in the order of mild, moderate, severe, unknown and total. A

subject will be counted only once at the maximum severity within each system organ class and preferred term.)

11. AEs by maximum severity by preferred term (by treatment group) (Preferred terms will be presented in decreasing frequency order. Maximum severity will be presented within each preferred term in the order of mild, moderate, severe, unknown and total. A subject will be counted only once at the maximum severity within each preferred term.)
12. Related AEs by system organ class and preferred term
13. SAEs by system organ class and preferred term
14. SAEs by preferred term
15. Related SAEs by system organ class and preferred term
16. AEs that led to discontinuation of study treatment by system organ class and preferred term
17. AEs that led to withdrawal from study by system organ class and preferred term
18. SAEs with fatal outcome by system organ class and preferred term
19. AEs that occurred within 2 hours from infusion start by system organ class and preferred term (by treatment group)
20. AEs by12 weeks intervals from first infusion to the end of study by system organ class and preferred term (by treatment group)
21. Pre-treatment SAEs that occurred since screening and prior to first infusion by system organ class and preferred term

The following listings will be provided.

1. Listing of AEs
2. Listing of SAEs
3. Listing of AEs that led to discontinuation of study treatment
4. Listing of AEs that led to withdrawal from study
5. Listing of AEs that occurred within 2 hours from infusion start
6. Listing of AEs related to PET ligands
7. Listing of SAEs with fatal outcome
8. Listing of AEs for subjects with treatment-emergent positive anti-BIIB037 antibody

4.5.2.2 Incidence rate analysis

Follow-up adjusted incidence rate for the placebo-controlled period will be summarized by system organ class and preferred terms both by treatment group and by treatment group stratified by ApoE status.

4.5.2.3 Subgroup analysis for protocol version 4

Due to the change in maximal dose from 6 mg/kg to 10 mg/kg for ApoE ε4 carrier high dose group in protocol version 4, not all subjects have had opportunity to receive the protocol specified high dose (6 doses in titration before receive 10mg/kg) in the placebo-controlled period. Incidence tables of AEs and SAEs will be provided for ApoE ε4 carriers who were randomized to the high dose group, stratified by the expected number of doses at 10 mg/kg (categories of 0, 1-6, 7-13, 14, and a total column of having at least one dose) a subject would have received based on the first infusion date and the date consenting to protocol version 4. Randomization treatment groups will be used for this analysis.

4.5.3 ARIA – AE of special interest

4.5.3.1 Background

ARIA is an AE of special interest in this study. Please see protocol section 7.2.1 for ARIA management and dose disposition guidelines. Since ARIA is a brain MRI finding, ARIA data are collected under two data sources: (1) safety MRI data as recorded on brain MRI worksheet by central MRI reader; (2) AE eCRF. For each ARIA event, the information of start/end date, severity, locations in brain regions and status on MRI scan is collected on the brain MRI worksheet by central MRI reader. ARIA severity is determined by central MRI reader based on number and size of the ARIA regions on imaging. An AE record is then entered into the eCRF by the investigator with the start/end date and severity information from brain MRI worksheet, and with information on the symptomatic status and action taken towards study drug. If ARIA is symptomatic, the symptoms will be entered into AE eCRF and the severity of the symptoms will be determined by the investigator. AE eCRF data will be used as the primary source for ARIA analysis as it contains the complete information of ARIA as well as associated symptoms. Safety MRI data will also be used to show the consistency between two data sources, provide details on MRI assessments, and for any specific analysis that requires information from MRI.

ARIA includes ARIA-E (vasogenic edema) and ARIA-H (hemorrhage). ARIA-H includes ARIA-H microhemorrhage, ARIA-H macrohemorrhage and ARIA-H superficial siderosis. Table 6 shows the reported term on MRI worksheet, the corresponding reported term on AE eCRF, and the MedDRA preferred term and lower level term for each type of ARIA.

Table 6: Reported and MedDRA terms for ARIA

Reported term on MRI worksheet	Reported term on AE eCRF	MedDRA version 21.0 preferred term	MedDRA version 21.0 lower level term
ARIA-E	Asymptomatic ARIA-E Symptomatic ARIA-E	Amyloid related imaging abnormality-oedema/effusion	ARIA-E

ARIA-H microhemorrhage	Asymptomatic ARIA-H (Microhemorrhage) Symptomatic ARIA-H (Microhemorrhage)	Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	ARIA-H
ARIA-H macrohemorrhage	Asymptomatic ARIA-H (Macrohemorrhage) Symptomatic ARIA-H (Macrohemorrhage)	Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	ARIA-H
ARIA-H superficial siderosis	Asymptomatic ARIA-H (Superficial Siderosis) Symptomatic ARIA-H (Superficial Siderosis)	superficial siderosis of the central nervous system	superficial siderosis of the central nervous system

For any specific ARIA event, the start date of the duration based on MRI is the date of the MRI assessment that initially identifies the ARIA event, and the end date of the duration based on MRI is the date of the MRI assessment that shows the complete resolution of this ARIA event (in the case of ARIA-E), or the date of the MRI assessment that shows ARIA being stable (in the case of ARIA-H). Stable was defined as 'No change' or 'decrease' in number, size, severity or number of locations between 2 consecutive MRIs including the initial detection MRI and the follow-up MRIs.

For symptomatic ARIA events, if there is any related symptom that proceeds the first MRI identification, then the symptom onset date will be used as the start date of the symptomatic ARIA duration. The end date of the symptomatic ARIA duration will be the date of the resolution or stable MRI as defined above for the duration based on MRI.

If the severity increases, or the event changes from asymptomatic to symptomatic, or from non-serious to serious, more than one AE records will be added to eCRF to capture the change with new start/end AE dates (the end date of the previous record will be the start date of the next record). For analysis, records with changes in severity or symptomatic status or seriousness are considered as a single ARIA event. The severity/symptomatic status/seriousness for that event is defined as the worst level among all the AE records that belong to that event.

If the same type of ARIA event happens again after the previous event has ended, then it is considered a recurrent event of ARIA of that type. Recurrent events will be referred as the second event, the third event, and etc.

If the duration based on MRI of an ARIA-E event overlaps with the duration based on MRI of an ARIA-H event, then these 2 ARIA events are considered as concurrent events.

4.5.3.2 Incidence and summary of ARIA

Incidence of ARIA-E, ARIA-H, ARIA-E and ARIA-H (not necessarily concurrent), concurrent ARIA-E and ARIA-H, ARIA-E or ARIA-H, isolated ARIA-H (only ARIA-H, no ARIA-E), ARIA-H microhemorrhage, ARIA-H macrohemorrhage and ARIA-H superficial siderosis will be summarized based on both AE eCRF and MRI data. If there is any discrepancy in incidence between the two data sources, a listing of the subjects and ARIA events with discrepancy will be provided. In addition, the incidence table based on AE eCRF source will also be done by treatment group (placebo, low dose, high dose and BIIB037 total; analysis display A in Appendix 6.1).

Number of subjects with each type of ARIA, maximum severity and worst symptomatic status of the type of ARIA being analyzed will be summarized based on AE eCRF. For subjects with symptomatic ARIA, the maximum severity of symptoms will also be summarized.

Number of subjects with ARIA-H microhemorrhage events post-baseline (broken down by categories of 1-4, 5-9 and >=10) stratified by whether they have had microhemorrhage at baseline will be summarized based on safety MRI data. The summary will be conducted based on the MRI that shows the maximum number of microhemorrhages as well as the last MRI in the study period.

Summary of concurrent ARIA-E and ARIA-H will be provided including the following information: number of subjects with concurrent ARIA-E and ARIA-H (and further broken down to each type of ARIA-H), the severity of ARIA-E based on MRI, the symptomatic status of ARIA-E, the severity of symptoms based on AE eCRF. For subjects with recurrent ARIA-E events, if there is an event concurrent with ARIA-H, it will be used for the summary, and the first concurrent event will be used if there are more than one event concurrent with ARIA-H.

An incidence table of AEs considered by the investigator to be related to ARIA by system organ class and preferred term for subjects with symptomatic ARIA will be provided, as well as a listing of these AEs. Similarly, an incidence table of AEs related to ARIA for subjects with symptomatic ARIA and severe symptoms will be provided, as well as a listing of these AEs.

Listings of AE records for each type of ARIA events and listings of MRI assessments for subjects with each type of ARIA events will be provided.

Montreal Cognitive Assessment (MOCA) is performed at baseline and at each unscheduled ARIA monitoring visit for ARIA subjects (approximately every 4 weeks) except for mild asymptomatic microhemorrhage subjects. An incidence table of subjects with ARIA events whose MOCA total scores decrease 2 points or more from baseline will be provided. A listing of MRI assessments and MOCA total scores for subjects with ARIA events will be provided.

Line plots of MMSE mean change from baseline values and standard errors at each planned visit (baseline, Week 26, Week 50 and Week 78) will be provided by treatment group stratified by ApoE status and with stratification on the following factors:

(1) ARIA-E severity based on MRI. The groups are: subjects without ARIA-E, subjects with mild ARIA-E, subjects with moderate ARIA-E and subjects with severe ARIA-E.

(2) Within ARIA-E subjects, stratify by the severity of the concurrent symptoms based on AE eCRF. The groups are: subjects without symptoms, subjects with mild symptoms, subjects with moderate symptoms, and subjects with severe symptoms.

For subjects with recurrent ARIA-E events, the first ARIA-E event will be used for the classification for each of the factors.

4.5.3.3 Summary of recurrent ARIA-E

Follow-up adjusted incidence rate of subjects with ARIA-E, with 2 or more events of ARIA-E, with 3 or more events of ARIA-E and with more than 3 events of ARIA-E based on their entire follow-up time will be summarized based on AE eCRF. The entire follow-up time is from the first dose until the last day in the placebo-controlled period.

Number of total ARIA-E events and the MRI severity of each event will be summarized based on AE eCRF. Number of total symptomatic ARIA-E events, the MRI severity of each symptomatic event and the severity of the symptoms of each symptomatic event will be summarized based on AE eCRF.

Summary of first ARIA-E events table based on AE eCRF will summarize the number of subjects with a first event of ARIA-E, the MRI severity of the events, the symptomatic status of the events, the severity of the symptoms for symptomatic events, whether SAE or not, number of resolved and unresolved events, duration of the resolved events, time from first infusion in study (active or placebo) to onset, number of doses received since the start of the study to onset, dose level of the last infusion received prior to onset, dosing status (continue as planned, dose interrupted, dose reduced, or dose discontinued) after the events, and the number of subjects with recurrent ARIA-E events. The same summary of first ARIA-E events table will also be done on subjects who had recurrent ARIA-E events.

Summary of recurrent ARIA-E events table based on AE eCRF will summarize the following information for both the second and third event of ARIA-E events: the number of subjects with the previous event of ARIA-E, the number of subjects with at least one dose and one MRI after the previous ARIA-E resolution, the number of subjects with this event of ARIA-E, the MRI severity of the events, the symptomatic status of the events, the severity of the symptoms for symptomatic events, whether SAE or not, number of resolved and unresolved events, duration of the resolved events, time from first infusion in study (active or placebo) to onset, time from previous resolution to onset, number of doses received since the start of the study to onset, dose level of the last infusion received prior to onset, dosing status (continue as planned, dose interrupted, dose reduced, or dose discontinued) after the events. The number of subjects with more than 3 events of ARIA-E, and the number of subjects who discontinued study treatment after recurrent ARIA-E onset will also be summarized.

A listing of subjects who withdrew from the study with unresolved ARIA-E or subjects with ongoing ARIA-E at the time of data cutoff (also considered as unresolved) will be provided with the details of the event including the duration from onset to last follow-up.

For subjects with recurrent ARIA-E, a listing of study drug administration, MRI assessments, severity and symptomatic status of each event, and end-of-treatment reason (if present) will be provided.

4.5.3.4 Exposure adjusted analysis

Exposure adjusted incidence rate of ARIA-E events will be summarized based on safety MRI data. The exposure adjusted follow-up time is from the first dose until the initial occurrence of ARIA-E for those who experienced ARIA-E, and until the end of follow-up for those who did not. Since ARIA is an MRI finding, the day of the last MRI assessment in the placebo-controlled period will be used as the end of follow-up for those who didn't experience the event.

Study drug administration information prior to first ARIA-E onset will be summarized for ARIA-E subjects, including number of total infusions, number of infusions at each dose level (placebo, 1 mg/kg, 3 mg/kg, 6 mg/kg and 10 mg/kg), dose level of the last infusion, maximum dose level received, and cumulative dose as a continuous variable.

4.5.3.5 Time to event analysis

Kaplan-Meier plot of time to first ARIA-E event will be produced based on safety MRI data. Time to event is calculated as date of the MRI assessment that initially detects ARIA-E event - date of first infusion (aducanumab or placebo) +1. Censor time for subjects without ARIA-E is calculated as date of last MRI assessment in the placebo-controlled period - date of first infusion (aducanumab or placebo) +1. Estimated proportion with ARIA-E and number of subjects at risk at selected timepoints will also be presented. The plot will be presented by treatment group stratified by ApoE status.

4.5.3.6 Subgroup analysis for protocol version 4

Due to the change in maximal dose from 6 mg/kg to 10 mg/kg for ApoE ε4 carrier high dose group in protocol version 4, not all subjects have had opportunity to receive the protocol specified high dose (6 doses in titration before receive 10mg/kg) in the placebo-controlled period. Incidence of ARIA events and summary of first ARIA-E events tables will be provided for ApoE ε4 carriers who were randomized to the high dose group, stratified by the expected number of doses at 10 mg/kg (categories of 0, 1-6, 7-13, 14, and a total column of having at least one dose) a subject would have received based on the first infusion date and the date consenting to protocol version 4. Randomization treatment groups will be used for this analysis.

4.5.4 Clinical Laboratory Data

The following clinical laboratory parameters are assessed in the protocol and will be analyzed:

- Hematology:
  - White blood cells (leukocytes), lymphocytes, neutrophils, monocytes, eosinophils, basophils
  - Red blood cells (erythrocytes), erythrocytes distribution width, erythrocytes mean corpuscular volume, erythrocytes mean corpuscular hemoglobin, erythrocytes mean corpuscular hemoglobin concentration

- Hemoglobin
- Hematocrit
- Platelet count

- Blood chemistry:
  - Liver: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, gamma-glutamyl-transferase (GGT)
  - Renal: blood urea nitrogen (BUN), creatinine
  - Electrolytes: sodium, potassium, chloride, bicarbonate
  - Other: glucose, calcium, phosphorus, albumin, uric acid, lactate dehydrogenase (LDH), total protein
- Urinalysis: specific gravity, potential of hydrogen (pH), color, blood, glucose, ketones, protein, white blood cells, red blood cells

4.5.4.1 Quantitative analyses

For numeric laboratory parameters, actual values, change from baseline and percent change from baseline will be summarized by visit. Number of evaluable subjects, mean, standard deviation, median, 25% and 75% quartiles, minimum and maximum values will be presented at each visit.

Plots of mean values (with standard error) for numeric laboratory parameters at each visit will be provided.

Listings of individual laboratory measurements by patients for all the parameters will be provided.

Visit windows for by visit summaries

For laboratory by visit summaries, the analysis visit should be defined using visit windows (see Table 7 below). If there is more than 1 value in the same analysis visit window for a certain parameter for a subject, then the closest record to the target visit day will be used for the by visit analysis. If there are 2 values in the same analysis visit window with the same distance from the target visit day for a certain parameter for a subject, then the record with the later date will be used for the by visit analysis. If there are 2 values on the same day for a certain parameter for a subject, then the record with the later time will be used for the by visit analysis.

Table 7: Visit Windows for Laboratory by Visit Summaries

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 24	169	[2, 252]
Week 48	337	[253, 420]
Week 72	505	[421, 525]

Analysis visit	Target visit day	Analysis visit window
Week 78	547	[526, the end day of the placebo-controlled period*]
* The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter LTE, and is the last day in study for subjects who do not enter LTE.		

4.5.4.2 Qualitative analyses

For all qualitative analyses, all values will be included (not just the "analyzed record" within each visit window in the quantitative analyses).

Shift analyses

Laboratory data will be summarized using shift tables where appropriate. Each subject's hematology, blood chemistry and urinalysis numeric values will be flagged as "low", "normal", or "high" relative to the normal ranges of the central laboratory or as "unknown" if no result is available. Each subject's urinalysis categorical values will be flagged as "positive" or "negative", or "unknown" if no value is available.

Shifts from baseline to high/low status will be presented for hematology, blood chemistry and urinalysis numeric parameters, and shifts from baseline to abnormal (positive) will be presented for urinalysis categorical parameters. Shift to low includes normal to low, high to low, and unknown to low; Shift to high includes normal to high, low to high, and unknown to high. Subjects need to have at least one post-baseline evaluation and a baseline value not low or high or positive (including missing) in order to be included in the analysis. A listing of laboratory normal ranges will be provided.

Grade analyses

Worst post-baseline grade will be summarized for each laboratory parameter in both exclusive way and cumulative way. Subjects need to have at least one post-baseline evaluation in order to be included in the analysis. Common Toxicity Criteria for Adverse Events v4.0.3 (CTCAE) published on 2010-06-14 will be used for grade determination. Grade determination is based solely on laboratory values not taking AEs into account.

Potentially Clinically Significant laboratory abnormalities analyses

For hematology, blood chemistry and urinalysis, the number of subjects with potentially clinically significant laboratory abnormalities post-baseline will be summarized for the parameters provided in Table 8. Subjects need to have at least one post-baseline evaluation and a baseline value not potentially clinically significant (including missing) in order to be included in the analysis.

Table 8: Criteria to Determine Potentially Clinically Significant (PCS) Laboratory Abnormalities

Clinical Laboratory Outlier Criteria		
Parameter name	**PCS Low**	**PCS High**
HEMATOLOGY		

Clinical Laboratory Outlier Criteria		
Parameter name	**PCS Low**	**PCS High**
White blood cells	<3.0 x 10^9/L	>16 x 10^9/L
Lymphocytes	<0.8 x 10^9/L	>12 x 10^9/L
Neutrophils	<1.5 x 10^9/L	>13.5 x 10^9/L
Monocytes	N/A	>2.5 x 10^9/L
Eosinophils	N/A	>1.6 x 10^9/L
Basophils	N/A	>1.6 x 10^9/L
Red blood cells	≤3.5 x 10^{12}/L	≥6.4 x 10^{12}/L
Hemoglobin - Females	≤95 g/L	≥175 g/L
Hemoglobin - Males	≤115 g/L	≥190 g/L
Hematocrit - Females	≤32%	≥54%
Hematocrit - Males	≤37%	≥60%
Platelet count	≤75 x 10^9/L	≥700 x 10^9/L
BLOOD CHEMISTRY		
Alanine aminotransferase (ALT)	N/A	>3 x ULN
Aspartate aminotransferase (AST)	N/A	>3 x ULN
Alkaline phosphatase (ALP)	N/A	>3 x ULN
Total bilirubin	N/A	>1.5 x ULN
Blood urea nitrogen (BUN)	N/A	≥10.7 mmol/L
Creatinine	N/A	≥176.8 umol/L
Sodium	≤126 mmol/L	≥156 mmol/L
Potassium	≤3 mmol/L	≥6 mmol/L
Chloride	≤90 mmol/L	≥118 mmol/L
Bicarbonate	≤16 mmol/L	≥35 mmol/L
Glucose	≤2.2 mmol/L	≥9.7 mmol/L
Calcium	≤2 mmol/L	≥3 mmol/L
Phosphorus	≤0.6 mmol/L	≥1.7 mmol/L
Albumin	≤25 g/L	≥625 g/L
Total protein	≤45 g/L	≥100 g/L
URINALYSIS		
Glucose	N/A	≥ ++++
Ketones	N/A	≥ ++++
Protein	N/A	≥ ++
ULN = upper limit of normal		

Potential serious hepatotoxicity

Potential serious hepatotoxicity is defined as ALT or AST > 3x ULN and total bilirubin > 2x ULN at any time post-baseline, not necessarily concurrent. A scatterplot of the maximum post-baseline ALT or AST value relative to ULN and maximum post-baseline total bilirubin value relative to ULN (not necessarily concurrent) for each subject will be provided. A line plot of ALT, AST, ALK and total bilirubin values over time for subjects with potential serious hepatotoxicity will be provided. In addition, subjects with ALT > 1x ULN, >3x ULN, >5x ULN, >10x ULN or >20x ULN, subjects with AST > 1x ULN, >3x ULN, >5x ULN, >10x ULN or >20x ULN, subjects with total bilirubin >1x ULN or >2x ULN, subjects with ALP >1x ULN or >1.5x ULN, and subjects with AST or ALT > 3x ULN post-baseline accompanied by concurrently elevated total bilirubin >1.5x ULN or > 2x ULN will be presented. Concurrent is defined as on the same day. A listing of subjects with potential serious hepatotoxicity will be provided.

4.5.5 C-SSRS Data

The Columbia Suicide Severity Rating Scale (C-SSRS) is an assessment that evaluates suicidal ideation and behavior. There are 5 "Yes/No" questions on suicidal ideation following the increasing severity order: (1) Wish to be dead, (2) Non-specific active suicidal thoughts, (3) Active suicidal ideation with any methods (not plan) without intent to act, (4) Active suicidal ideation with some intent to act, without specific plan, (5) Active suicidal ideation with specific plan and intent, and 6 "Yes/No" questions on suicidal behavior following the increasing severity order: (6) Preparatory acts or behavior, (7) Aborted attempt, (8) Interrupted attempt, (9) Actual attempt, (10) Suicidal behavior, (11) Suicide (only at post-baseline visits). Another "Yes/No" question of whether the subject has engaged in non-suicidal self-injurious behavior is also collected.

In the summary table for C-SSRS, number of subjects who answered "Yes" to each of the 11 questions post-baseline, subjects who answered "Yes" to at least one question for suicidal ideation, subjects who answered "Yes" to at least one question for suicidal behavior, and subjects who have engaged in non-suicidal self-injurious behavior will be presented. A listing of subjects with any suicidal ideation or behavior at baseline or post-baseline will be provided.

4.5.6 ECG Data

Shift from normal or unknown ECG at baseline to abnormal, not adverse event or abnormal, adverse event post-baseline ECG will be summarized for the placebo-controlled period. Subjects with abnormal post-baseline ECG status will be listed.

4.5.7 Vital Sign Data

Vital sign parameters include body temperature, systolic blood pressure, diastolic blood pressure, heart rate, respiration rate and weight. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes. The descriptive statistics for actual values and change from baseline will be summarized at each visit. Plot of mean vital sign values at each visit will be provided.

The analysis of vital signs will also focus on the incidence of clinically relevant outliers based on the following criteria. The incidence and percentage of clinically relevant outliers determined by each criterion will be summarized. A listing of subjects with clinically relevant vital signs will be provided.

Table 9: Criteria Used to Assess Potential Clinically Relevant Outliers in Vital Signs

Variable	Low	High
Systolic Blood Pressure	<90 mm Hg or ≥20 mm Hg decrease from Baseline (BL)	>180 mm Hg or ≥20 mm Hg increase from BL

Diastolic Blood Pressure	< 50 mm Hg or ≥15 mm Hg decrease from BL	>105 mg Hg or ≥15 mm Hg increase from BL
Heart Rate	<50 bpm or ≥ 15 bpm decrease from BL	>120 bpm or ≥ 15 bpm increase from BL
Temperature	>2 degree C decrease from BL	>38.5 C or >2 degrees C increase from BL
Respiration Rate	< 10 breaths per minute or ≥ 50% decrease from BL	>25 breaths per minute or ≥50% increase from BL
Weight	≥7% decrease from BL	≥7 % increase from BL
BL= baseline; bpm = beats per minute		

Visit windows for by visit summaries

For vital sign by visit summaries, the analysis visit should be defined using windows (see Table 10 below). If there is more than 1 value in the same analysis visit window for a certain parameter for a subject, then the closest record to the target visit day will be used for the by visit analysis. If there are 2 values in the same analysis visit window with the same distance from the target visit day for a certain parameter for a subject, then the record with the later date will be used for the by visit analysis.

Table 10: Visit Windows for Vital Sign by Visit Summaries

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 4	29	[2, 42]
Week 8	57	[43, 70]
Week 12	85	[71, 98]
Week 16	113	[99, 126]
Week 20	141	[127, 154]
Week 24	169	[155, 182]
Week 28	197	[183, 210]
Week 32	225	[211, 238]
Week 36	253	[239, 266]
Week 40	281	[267, 294]
Week 44	309	[295, 322]
Week 48	337	[323, 350]
Week 52	365	[351, 378]
Week 56	393	[379, 406]
Week 60	421	[407, 434]
Week 64	449	[435, 462]
Week 68	477	[463, 490]
Week 72	505	[491, 518]
Week 76	533	[519, the end day of the placebo-controlled period*]
* The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter LTE, and is the last day in study for subjects who do not enter LTE.		

4.6 Pharmacokinetics Analysis

The PK analysis population will be used for the description of the concentration-time profiles and for the estimation of PK parameters. Randomization treatment groups will be used for

PK analysis. Tables and figures, if not otherwise specified, will be presented by treatment group stratified by ApoE status (3 columns under each treatment group: ApoE ε4+, ApoE ε4- and total; analysis display B in Appendix 6.1). Listings will be presented by treatment group stratified by ApoE status.

PK evaluation will be based on the concentration of aducanumab in serum samples collected prior to infusion and between 10 and 60 minutes after completion of the infusion and line flush for the visits specified per protocol.

Concentrations of aducanumab that are below the limit of quantification (BLQ) will be imputed as 0. When summarizing concentrations or PK parameters in serum, a minimum of 2 values are required to show the arithmetic mean and geometric mean, and at least 3 values are required to show the standard deviation and coefficient of variation.

4.6.1 Serum Concentration Profile

Serum concentration data will be summarized by nominal visit. Number of evaluable subjects, arithmetic mean, standard deviation, median, 25% and 75% quartiles, minimum, maximum, geometric mean, and coefficient of variation will be presented at each visit. A listing of individual concentration data will be provided.

A semi-logarithmic plot of the mean serum concentration-time curves of aducanumab from first visit to last visit through nominal times will be provided.

4.6.2 Serum PK Parameters

Two PK parameters C_{max} and C_{min} will be computed by noncompartmental methods, as data permit, from serum concentration-time data:

Parameter	Definition	Units
C_{max}	Observed maximum serum aducanumab concentration	ug/mL
C_{min}	Observed minimum serum aducanumab concentration	ug/mL

Number of evaluable subjects, arithmetic mean, standard deviation, median, 25% and 75% quartiles, minimum, maximum, geometric mean, and coefficient of variation will be presented for the PK parameters.

4.6.3 Subgroup analysis for protocol version 4

Due to the change in maximal dose from 6 mg/kg to 10 mg/kg for ApoE ε4 carrier high dose group in protocol version 4, not all subjects have had opportunity to receive the protocol specified high dose (6 doses in titration before receive 10mg/kg) in the placebo-controlled period. Summary tables for serum concentration and PK parameters will be provided for ApoE ε4 carriers who were randomized to the high dose group, stratified by the expected number of doses at 10 mg/kg (categories of 0, 1-6, 7-13, 14, and a total column of having at least one dose) a subject would have received based on the first infusion date and the date consenting to protocol version 4.

4.7 Immunogenicity Analysis

4.7.1 Background

Definition of baseline value

Baseline value is defined as the latest immunogenicity data collected prior to the first dose. If no immunogenicity data are collected prior to the first dose, baseline value is missing and will be imputed as anti-drug antibody negative for immunogenicity analyses.

Treatment-emergent anti-aducanumab antibody positive responses

Post-baseline positive anti-aducanumab antibody responses are defined as treatment-emergent if a subject is either (1) antibody negative at baseline; or (2) antibody positive at baseline but the post-baseline antibody response is more than 2-fold increase in titer compared to the baseline response.

Persistent and transient positive responses for the placebo-controlled period

Subjects with treatment-emergent positive anti-aducanumab antibody responses in the placebo-controlled period will be further classified as transient positive, if only a single positive evaluation occurs or more than 1 positive evaluation but occur with < 112 days (16 weeks) apart, or as persistent positive, if more than one consecutive positive evaluation occurs ≥ 112 days (16 weeks) apart or a positive evaluation occurs at the last available time point with no further negative results available (including long-term extension).

4.7.2 Immunogenicity analysis

Immunogenicity population will be used to analyze immunogenicity data. Safety treatment groups will be used for immunogenicity analysis. Tables will be presented by treatment group (placebo, low dose, high dose and BIIB037 total; analysis display A in Appendix 6.1). Listings will be presented by treatment group stratified by ApoE status.

A summary table of subjects with treatment-emergent positive anti-aducanumab antibody responses results will be provided. The number and percentage of anti-aducanumab positive responses will be summarized at each visit and at any time post-baseline. Subjects with persistent response and subjects with transient response will be presented. A listing of subjects with anti-aducanumab antibody positive results will also be provided.

Visit windows for by visit summaries

For immunogenicity by visit summaries, the analysis visit should be defined using visit windows (see Table 11Table 7 below). If there is more than 1 value in the same analysis visit window for a subject, then the closest record to the target visit day will be used for the by visit analysis. If there are 2 values in the same analysis visit window with the same distance

from the target visit day for a certain parameter for a subject, then the record with the later date will be used for the by visit analysis. If there are 2 values on the same day for a certain parameter for a subject, then the record with the later time will be used for the by visit analysis.

Table 11: Visit Windows for Immunogenicity by Visit Summaries

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 24	169	[2, 196]
Week 32	225	[197, 308]
Week 56	393	[393, 470]
Week 78	547	[470, the end day of the placebo-controlled period*]
* The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter LTE, and is the last day in study for subjects who do not enter LTE.		

4.8 Additional Exploratory Endpoints

4.8.1 Biomarker

Analyses for structural MRI, tf-fMRI, ASL-MRI, tau PET, CSF biomarkers and blood biomarkers will be specified in a separate SAP for biomarker analysis.

4.8.2 Health Outcomes

Analyses for informant/care partner's own EQ-5D index-score (IR-I) and CAM will be provided in a separate document.

5 INTERIM ANALYSIS

An interim analysis will occur after approximately 50% of the subjects have had the opportunity to complete the Week 78 visit for both 221AD301 and 221AD302. To maintain the integrity of the study in the event of the interim analysis, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim analysis. The IDMC will review the unblinded results of the interim analysis provided by the independent group and will make a recommendation to Biogen based on pre-specified criteria.

An interim analysis for futility of the primary endpoint will be performed to allow early termination of the studies if it is evident that the efficacy of aducanumab is unlikely to be achieved. The futility criteria will be based on conditional power, which is the chance that the primary efficacy endpoint analysis will be statistically significant in favor of aducanumab at the planned final analysis, given the data at the interim analysis. The conditional power is calculated assuming that the future unobserved effect is equal to the maximum likelihood estimate of what is observed in the interim data:

$$CP\left(Z(1) \geq Z_\alpha \middle| Z(t)\right) = 1 - \phi\left(\frac{Z_\alpha\sqrt{n_2} - Z(t)\sqrt{n_1}}{\sqrt{n_2 - n_1}} - \frac{Z(t)\sqrt{n_2 - n_1}}{\sqrt{n_1}}\right)$$

where t is the fraction of information and $Z(t)$ is the observed Z-statistic at the interim analysis, $Z(1)$ is the Z-statistic and α is the type I error at the final analysis, n_1 and n_2 are the number of subjects at the interim and at the final analysis, respectively.

The futility decision will primarily be based on the conditional power for the primary efficacy endpoint. The study will not be considered as futile unless both studies 221AD301 and 221AD302 have conditional power for the primary efficacy endpoint less than 20% in both the high-dose and low-dose treatment groups. Given the insufficient knowledge of aducanumab's potential effects on various functional/cognition endpoints or in certain subgroups at the present time, other data in addition to the pre-specified futility criteria will be considered as well, and the IDMC may recommend the studies to be continued as planned based on the weight of the evidence.

An interim analysis for superiority may be performed, to allow the possibility to demonstrate the treatment effect early. If an interim analysis for superiority is performed, the O'Brien-Fleming stopping boundary will be used. If an interim analysis for superiority is not performed, then no alpha adjustment will be used for the final analysis after all subjects have had the chance to complete the Week 78 visit.

6 APPENDIX

6.1 Analysis Display

Analysis display A

Placebo	BIIB037 low dose	BIIB037 high dose

Analysis display B

Placebo			BIIB037 low dose			BIIB037 high dose		
ApoE e4+ placebo	ApoE e4- placebo	Total	ApoE e4+ 3 mg/kg	ApoE e4- 6 mg/kg	Total	ApoE e4+ 10 mg/kg	ApoE e4- 10 mg/kg	Total

6.2 Protocol Deviation Classification

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

6.3 Implementation of the Copy Increment from Reference and Pattern Mixture Model

6.3.1 Copy Increment from Reference

The dataset will first be imputed to monotone missing using PROC MI with the MCMC and impute=monotone option. Imputation will be carried out 1000 times and any internal missing observations, including missing baseline covariates and intermediate missing in the response variable will be replaced with the average across all imputations.

For the resulted data with monotone missing, the following steps will be used to create imputed datasets:

(1) Data from all patients will be used to fit a multivariate normal distribution with unstructured mean and unstructured variance using a Bayesian approach with a noninformative prior for the mean and a conjugate prior for the variance covariance matrix.
(2) Draw a pseudo-independent sample for the linear predictor parameters and the covariance parameters from the joint posterior distribution obtained in step (1). Both steps (1) and (2) will be done using PROC MCMC in SAS.
(3) Use the linear predictor parameters and the covariance parameters obtained in step (2) to construct new mean vectors separately for each treatment group (placebo, aducanumab low dose, aducanumab high dose). Specifically, the newly constructed mean vector for someone on treatment group T whose last observed visit was visit k is calculated as

$$\mu_T^{(k)} = \begin{cases} \mu_{i,T}, & if\ i \le k \\ \mu_{k,T} - \mu_{k,P} + \mu_{i,P}, & if\ i > k \end{cases}$$

Here P represents the placebo group. For patients with no post-baseline records, or patients on the placebo group, the newly constructed mean vector is the same as the placebo mean.
(4) Using $\mu_T^{(k)}$ from step (3) and covariance parameters from step (2), find the conditional normal distribution of the visit with missing data, and use this conditional distribution to impute the missing data.

6.3.2 Pattern Mixture Model

Subjects will be assigned one of the following three patterns:

1. Completer: subjects with no missing data at Week 26, 50 and 78
2. Subjects who withdrew due to reasons that may be related to efficacy, including consent withdrawn, withdrawal by parent/guardian, investigator decision, loss of capacity, change of treatment, and disease progression;
3. All the other subjects with missing data.

The dataset will first be imputed to monotone missing using PROC MI with the MCMC and impute=monotone option. Imputation will be carried out 1000 times and any internal missing observations, including missing baseline covariates and intermediate missing in the response variable will be replaced with the average across all imputations.

For the resulted data with monotone missing, the following steps will be used to create imputed datasets:

(1) Subset subjects in pattern 1 and pattern 2, and impute the missing data using the copy increment from reference method described in Section 6.3.1.
(2) Subset subjects in pattern 1 and pattern 3, and impute the missing data using PROC MI with the MONOTONE REG option.
(3) Combined datasets obtained in steps (1) and (2).

7 REFERENCES

Carpenter JR, Roger JH, Kenward MG. Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat. 2013;23(6):1352-71.

Hansen RA, Gartlehner G, Lohr KN, et al. Functional outcomes of drug treatment in Alzheimer's disease: A systematic review and meta-analysis. Drugs & aging. 2007;24(2):155-67.

ICH E9 (R1): Addendum to statistical principles for clinical trials on choosing appropriate estimands and defining sensitivity analyses in clinical trials. Endorsed by the ICH Steering Committee. 2014.

ICH E9 (R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials. European Medicines Agency. 2017.

Li, J. and Barlas, S. Divergence effect analysis in disease-modifying trials. Statistics in Biopharmaceutical Research. 2017; 9: 390-398.

Li, K. H. (1988), "Imputation Using Markov Chains," *Journal of Statistical Computation and Simulation*, 30, 57–79.

Little, R.J.A. (1993). Pattern‐mixture models for multivariate incomplete data. *Journal of the American Statistical Association, 88* , 125-134.

Little, R.J.A. (1994). A class of pattern‐mixture models for normal missing data. *Biometrika, 81*, 471-483.

Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993;43(11):2412–2414.

Mueller SG, Weiner MW, Thal LJ, et al. The Alzheimer's Disease Neuroimaging Initiative. In: Pettrella JR, Doraiswamy PM, eds. Neuroimaging Clinics of North America: Alzheimer's Disease: 100 Years of Progress. Philadelphia: Elsevier Saunders; 2005:869–877.

Rockwood K. The measuring, meaning and importance of activities of daily living (ADLs) as an outcome. Int Psychogeriatr. 2007;19(3):467-82. Epub 2007/03/15.

Rubin, D. B. (1976) “Inference and missing data.” Biometrika, 63(3), 581-592.

Rubin D.B. Multiple Imputation for Nonresponse in Surveys. John Wiley & Sons. 1987.

Schafer J.L. Analysis of Incomplete Multivariate Data. Chapman and Hall, New York. 1997.

Tractenberg RE, Weiner MF, Cummings JL, Patterson MB, Thal LJ. Independence of changes in behavior from cognition and function in community-dwelling persons with

Alzheimer's disease: a factor analytic approach. J Neuropsychiatry Clin Neurosci. 2005;17(1):51–60.

van Ginkel, J. R., Sijtsma, K., van der Ark, L. A., & Vermunt, J. K. (2010). Incidence of missing item scores in personality measurement, and simple item-score imputation. *Methodology: European Journal of Research Methods for the Behavioral and Social Sciences, 6*(1), 17-30.

Yan, X., Lee, S., and Li, N. (2009), "Missing data handling methods in medical device clinical trials," Journal of Biopharmaceutical Statistics, 19(6), 1085-1098.

Zucker, D. M., Wittes, J. T., Schabenberger, O. and Brittain, E. Internal pilot studies II: comparison of various procedures. Statistics in Medicine. 1999;18: 3493–3509.

STATISTICAL ANALYSIS PLAN
Addendum

Product Studied: Aducanumab
Protocol Number: 221AD301

A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease

Protocol Version: Version 6.0
Date of Protocol: 28 Jun 2018

Date of Statistical Analysis Plan Addendum: 4 Nov 2019, Final V1.0

Written By:	PPD	4 Nov 2019 Date
		04 Nov 2019 Date
Approved By:		4 Nov 2019 Date
		4. Nov 2019 Date
		4 Nov. 2019. Date

1 Modifications for Efficacy Analysis

The primary analysis will be conducted in the intent-to-treat (ITT) population, excluding data collected after 20 March 2019. The mixed model repeated measures (MMRM) model remains the same as before.

Unless otherwise specified, data collected after 20 March 2019 will be excluded for all the analysis of the primary and secondary endpoints, and the tertiary endpoints for efficacy and quality of life.

The following analyses will be conducted for the primary and secondary endpoints as supplementary analysis.

- Opportunity-to-Complete (OTC) analysis:
  The MMRM model in primary analysis will be repeated in the OTC population, defined as the ITT population that have had the opportunity to complete Week 78 by 20 March 2019.
- ITT analysis during the double-blind period:
  The MMRM model in primary analysis will be repeated in the ITT population with all the data collected until 17 April 2019 (Biogen released treatment assignments to IQVIA team on 18 April 2019 to be distributed to site upon request). Efficacy data collected up to 17 April 2019 will be mapped to analysis visits according to the pre-specified analysis definition (Table 3 in SAP v1.0 Section 4.3.1).

  The assessments collected after the futility announcement (21 March 2019) may deviate from the efficacy data schedule defined in protocol. Given the width of the pre-specified analysis visit window, an assessment may be mapped to an analysis visit even though the data collection day is far away from the target day of that analysis visit. In addition to the above analysis using the pre-specified analysis visits, analysis will also be conducted after data collected post 20 March 2019 being extrapolated to the closest analysis visit target day if the difference between the data collection day and the visit window target day exceeds 28 days. For example, if a subject's CDR-SB at the end-of-treatment (EOT) visit (after 20 March 2019) was collected on Day 480, the score will be extrapolated to Day 547 (the target day of Week 78) for analysis.
- Uncensored ITT analysis:
  The MMRM model in primary analysis will be repeated in the ITT population with all the data collected during the study, using the pre-specified analysis visits without extrapolation and using the analysis visits corrected by extrapolation, respectively.

Rationale for modifications:

The study was terminated on 21 March 2019 after a futility analysis. The treatment was stopped immediately upon the futility announcement for all subjects. Although assessments for efficacy and quality of life continued to be collected after the futility announcement at the

end-of-treatment visit and safety follow-up visit, these data may introduce bias due to assessments possibly being altered by knowledge of the futility declaration. The data collected after 20 March 2019 may also deviate from the planed schedule for efficacy/quality of life defined in protocol. Based on these considerations, the above modifications are made to the primary efficacy analysis, to include as many subjects and data as possible for analysis while minimizing potential bias in the results. The OTC analysis, ITT analysis during the double-blind period, and the uncensored ITT analysis are added to evaluate the robustness of the primary analysis results.

2 Other Modifications

The following change is in response to FDA's comments on SAP version 1.

- If the unstructured covariance matrix results in a lack of convergence in the mixed model for repeated measures (MMRM) and a structured covariance matrix is used, we will use the sandwich estimator to obtain the variance of the treatment effect estimator.