Statistical Analysis Plan

ISIS 814907–CS1

A Randomized, Double-Blind, Placebo-Controlled Study, Followed by an Open-Label Extension, to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 814907 in Patients with Mild Alzheimer's Disease

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Statistical Analysis Plan Signature Page

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Compound Name: 814907

Protocol: ISIS 814907-CS1

Study Title: A Randomized, Double-Blind, Placebo-Controlled Study, Followed by an Open-Label Extension, to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 814907 in Patients with Mild Alzheimer's Disease

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ABBREVIATION

Abbreviation	Definition
AD	Alzheimer's disease
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
aPTT	Activated partial thromboplastin time
ARWMC	Age-Related White Matter Changes
ASO	Antisense oligonucleotide
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
BP	Blood pressure
BUN	Blood urea nitrogen
CDR	Clinical Dementia Rating
CRF	Case Report Form
CSF	Cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Coefficient of variation
DTI	Diffusion Tensor imaging
ECG	Electrocardiogram
FAQ	Functional Assessment Questionnaire
FLAIR	Fluid-attenuated inversion recovery
FSE	Fast spin echo
FSMG	Formal Safety Monitoring Group
GDS	Geriatric Depression Rating Scale
GRE	Gradient echo
HR	Heart rate
LP	Lumbar puncture
LTE	Long-term extension
MAD	Multiple ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MHIS	Modified Hachinski Ischemic Scale
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
FSMG	Formal Safety Monitoring Group
INR	International normalized ratio
ISIS 814907	Antisense inhibitor of *MAPT*
IT	Intrathecal(ly)
ITT	Intent To Treat
mRNA	Messenger ribonucleic acid
NPI-Q	Neuropsychiatric Inventory Questionnaire
PET	Positron emission tomography
PD	Pharmacodynamic(s)

PK	Pharmacokinetic(s)
PT	Prothrombin time
QTcF	QT time corrected using the Friderica's method
QTcB	QT time using the Bazett's method
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
ROI	Region of interest
RR	Respiration rate
SAE	Serious adverse event
SBP	Systolic blood pressure
TEAE	Treatment-emergent adverse event
TSE	Turbo spin echo
WBC	White blood cell
WHO-DD	World Health Organization - Drug Dictionary

1. INTRODUCTION

This document provides a description of the study organization, study procedures, and the plan for the statistical analysis of the study data. Section 1 discusses study design, objectives, and endpoints; Section 2 provides the study procedures; Section 3 provides the detailed plan for the statistical analyses.

As with any statistical analysis plan (SAP), the proposed methods and approaches to the data analysis should be reviewed as flexible. The statistical analysis to some degree is iterative since so much of the planning is based on statistical and other assumptions, which require verification.

1.1 Study Overview

This is a Phase 1, multi-center, double-blind, randomized, placebo-controlled study of multiple IT bolus administrations of ISIS 814907 in patients with mild Alzheimer's Disease (AD) aged 50-74 years, inclusive.

This study is divided into 2 parts:

- Part 1: a randomized, double-blind, placebo-controlled multiple ascending dose (MAD) part, comprising a Screening Period of 8 weeks, a Treatment Evaluation Period of 13 weeks, and a Post-Treatment Period of 23 weeks
- Part 2: an open-label, long-term extension (LTE) part, comprising a Registration Period of 3 weeks (only for those who cannot transition seamlessly, i.e., patients from Cohorts A and B), a Treatment Evaluation Period of 48 weeks, and a Post-Treatment Period of 16 weeks (except in the UK (Amendment 7) where the Post-Treatment Period is 23 weeks)
    - For patients participating in Cohorts A and B there will be a variable gap of time between the end of Part 1 and entry into Part 2
    - Patients participating in Cohorts C and D will seamlessly transition from Part 1 to Part 2. Day 253 in Part 1 (i.e., last visit of Part 1 Post-Treatment Period) will correspond to Day -1 in Part 2 (i.e., first visit of Part 2 Treatment Evaluation Period).

Multiple Ascending Dose, Part 1

Four (4) ascending dose level cohorts (A, B, C, and D) of patients were enrolled sequentially and randomized with an overall ratio of 3:1 to receive ISIS 814907 or placebo. A sentinel dosing strategy was implemented. The first 2 patients at a given dose level were assigned 1:1 active: placebo, and at least 1 week elapsed between initiation of treatment in these 2 patients and initiation of treatment in additional patients at this dose level. The remaining patients were assigned to active or placebo at a 5:1 ratio for cohorts with N = 8, 8:2 ratio for cohorts with N = 12, or 11:3 ratio for cohorts with N = 16 to ensure a 3:1 active: placebo balance in each cohort. Based on the profile of effects observed in non-human primate toxicology studies, 24 hours is expected to be a sufficiently long observation period to identify possible safety

issues. Thus, as a safety measure, the sentinel dosing algorithm utilized for this study required that 1-week elapsed between initiation of treatment in the first 2 patients and initiation of treatment in subsequent patients in the cohort. Identified and potential risks associated with ISIS 814907 are described in detail in the Investigator's Brochure.

Initiation of dosing in a new cohort began after 3 conditions had been met: (1) all patients in the lower-dose cohorts have been enrolled, (2) at least 2/3 of the patients in the lower-dose cohort had been followed for at least 7 days after receipt of the fourth dose of Study Drug, and (3) a review of data (safety, PK, and PD data) collected in the lower-dose cohorts had been conducted by the Formal Safety Monitoring Group (FSMG) and a decision had been made to proceed with the next cohort.

Each patient in cohorts A, B and C received 4 doses of Study Drug with a 28-day interval between doses. In cohort D, the protocol prespecified 2 dosing regimen options: 1) four doses of Study Drug at 90 mg with a 28-day interval between doses or 2) two doses of Study Drug at 115 mg with an 84-day interval between doses. The FSMG selected the 115 mg x 2 dosing regimen. The planned dose regimens for the study are shown below. Based on emerging safety data from this study, the protocol permitted one or more cohorts to expand and enroll additional patients. PK and PD measures were collected at each dose level and compared to the results predicted by models constructed from preclinical data.

Cohort A: N = 8, mild AD, 10 mg ISIS 814907 or placebo × 4 doses
Cohort B: N = 8, mild AD, 30 mg ISIS 814907 or placebo × 4 doses
Cohort C: N = 12, mild AD, 60 mg ISIS 814907 or placebo × 4 doses
Cohort D: N = 16, mild AD, 90 mg ISIS 814907 or placebo × 4 doses *or* 115 mg ISIS 814907 or placebo × 2 doses

Following the 3-month Treatment Period, there was a 6-month Post-Treatment Period.

Long-Term Extension, Part 2

The ability for participants completing the MAD, Part 1, of the study to enter an open-label LTE, Part 2, of the study started with Cohort C. All patients in Cohorts C and D could seamlessly transition from Part 1 to Part 2. For patients in Cohorts C and D, Day 253 in Part 1 corresponded to Day -1 in Part 2. In Part 2, the Treatment Evaluation Period of 48 weeks was followed by a Post-Treatment Period of 16 weeks, except in the UK (Amendment 7) where the Post-Treatment Period was 23 weeks.

All patients will receive ISIS 814907 in Part 2 and will be dosed at an 84-day interval, regardless of the dose interval utilized in Part 1.

- Cohort C patients will continue the Cohort C dose (60 mg) with a quarterly (84-day) dose interval in the LTE, Part 2
- Cohort D patients will continue the Cohort D dose (115 mg) with a quarterly (84-day) dose interval in the LTE, Part 2.

- Cohort A and B patients who have completed the Treatment Evaluation and Post-Treatment Periods in Part 1 are also eligible to enter Part 2 of the study. For Cohorts A and B patients there will be a variable gap of time between the end of Part 1 and entry into Part 2. All Cohort A and B patients participating in the Part 2 LTE should be enrolled in Part 2 prior to the last patient in Cohort D entering Part 2 of the study. Cohorts A and B patients will receive the same dose as Cohort C patients (60 mg quarterly (84-day) doses).

Patients entering the LTE Part 2 will remain on the dose received when they initiate Part 2 unless ongoing review of the safety, PK/PD profile by the FSMG and the Sponsor require dose adjustments in individuals or for the entire study. The Treatment Evaluation Period of 48 weeks will be followed by a Post-Treatment Period of 16 weeks, except in the UK (Amendment 7) where the Post-Treatment Period is 23 weeks.

1.2 Objectives

1.2.1 Primary Objectives

To evaluate the safety and tolerability of ascending dose-levels of multiple intrathecal (IT) bolus administrations of ISIS 814907, an antisense inhibitor of *MAPT* messenger ribonucleic acid (mRNA) that encodes the tau protein, in patients with AD pathology.

1.2.2 Secondary Objective

To characterize the cerebrospinal fluid (CSF) pharmacokinetics (PK) of ascending dose-levels of multiple IT bolus administrations of ISIS 814907.

1.2.3 Exploratory Objectives

To explore effects of multiple doses of ISIS 814907 on potential target engagement and disease progression biomarkers and clinical endpoints relevant to AD. Plasma PK properties of ISIS 814907 will also be assessed. Evaluation of CSF total tau is key exploratory endpoint. If CSF total tau protein level, and/or CSF phospho-tau protein level, are reflective of target engagement, exploratory analyses will be conducted to characterize the relationships between dose, CSF PK, and CSF total tau and CSF phospho-tau protein levels. Disease progression clinical and biological markers are included primarily as a safety measure to document any marked worsening. A lesser objective is to gain experience with these measures in an ISIS 814907 clinical study as preparation for subsequent, longer-term clinical studies. It is not expected that the majority of biomarkers and clinical measures will be impacted significantly by the 3 months of ISIS 814907 administration planned for Part 1; however, the longer-term treatment with ISIS 814907 in Part 2 may affect both biomarkers and clinical measures.

1.3 Endpoints

There is no single primary endpoint for assessment of safety and tolerability, the primary objective of this study. This and other important endpoints are identified in the following sections.

1.3.1 Safety and Tolerability Endpoints

- Physical examination and standard neurological assessment (including fundi)
- Vital signs (Heart Rate [HR], Blood Pressure [BP], orthostatic changes, weight, respiratory rate, body temperature)
- Electrocardiograms (ECG)
- AEs and concomitant medications
- Columbia Suicide Severity Rating Scale (C-SSRS)
- CSF safety labs (cell counts, protein, albumin, glucose)
- Plasma laboratory tests (clinical chemistry, hematology)
- Urinalysis
- Safety MRI sequences (GRE T2 star, T2 FLAIR, T2 FSE/TSE, DTI)

Clinical evaluations (Section 3.7.3) and volumetric neuroimaging measures (Section 3.7.2.1) will be evaluated to monitor for unexpected deterioration.

1.3.2 Pharmacokinetic Endpoints

CSF samples are collected pre-dose on each injection day during the treatment period:

- Part 1: Days 1, 29, 57, and 85 for the 4-dose regimen, or Days 1 and 85 for the 2-dose regimen.
- Part 2: Days 1, 85, 169, 253, 337.

CSF samples are also collected during the Post-Treatment Period:

- Part 1: Days 113 and 141 for patients in Cohorts A and B, and Days 141 and 197 for patients in Cohorts C and D
- Part 2: Day 421

Plasma samples will be collected for PK analyses on the following days:

> **Part 1**: Days 1, 2, 29, 57, 85, and 86, during the Treatment Evaluation Period and on Days 113, 141, 169, 197 (patients in Cohorts C and D only) and 253 during the Post-Treatment Period

Part 2: Days 1, 2, 85, 169, 253, 337, and 338 during the Treatment Evaluation Period and on Days 421 and 449 during the Post-Treatment Period

Plasma post-distribution drug levels will be measured. C_{max} and area under the curve (AUC) will be determined, and elimination half-life will be assessed where appropriate.

1.3.3 Exploratory Endpoints

All endpoints in the study, including the exploratory endpoints serve as safety measures. While the below endpoints will be monitored for evidence of target engagement or PD effect, they will also be monitored to ensure the patient does not experience unexpected worsening during the study.

- Key exploratory endpoints
  - CSF total tau
    - Biochemical
  - Other potential CSF biomarkers may include, but are not limited to, target engagement (phospho-tau), A-beta42, A-beta40, neuronal injury markers (neurofilament light chain [NfL], phospho neurofilament heavy [pNfH], neuronal pentraxin, alpha-synuclein, visinin-like protein 1 [VILIP1]), synaptic markers (neurogranin [Ng], chromogranin B, synaptosomal-associated protein 25 [SNAP25]), innate immune activation markers (interleukin-6 [IL-6], tumor necrosis factor alpha [TNFα], interleukin-1 beta [IL-1β], monocyte chemoattractant protein-1 [MCP-1], S100B, chitinase-3-like protein 1 [YKL-40], complement [C3, factor H]), apolipoprotein E, clusterin, butyrylcholinesterase (BCHE), Potential blood/plasma biomarkers may include, but are not limited to NfL, pNfH, tau, IL-6, TNFα, 24S-hydroxycholesterol and uric acid
  - Neuroimaging
    - Structural MRI – Volumetric Analysis
      - Hippocampal, whole brain, intracranial and ventricle volumes
  - Exploratory MRI Analyses
    - Perfusion analysis – arterial spin labelling (ASL)
    - Diffusion analysis
    - Cortical thickness
    - White matter lesion analysis
    - CSF space analysis
  - PET (Cohorts C and D only in Part 1, and all patients in Part 2)
- Clinical Evaluations
  - Functioning/ability to perform activities of daily living
    - Functional Activities Questionnaire (FAQ)

- Cognitive
  - Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
  - Mini-mental state examination (MMSE)
  - Clinical Dementia Rating (CDR) Scale
- Neuropsychiatric
  - Neuropsychiatric Inventory - Questionnaire (NPI-Q)

Analyses may explore relationship between selected parameters (at baseline and their progression during the study) and genetic causes of AD (*APP, PSEN1, PSEN2*), potential genetic modifiers of disease phenotype (commonly occurring risk-associated SNPs of *APOE*, *BCHE*, *IL1RAP, CD33* and *MAPT H1* haplotype).

2. PROCEDURES

2.1 General Overview of Procedures

Ionis Pharmaceuticals, Inc. (or designee) will review all study data including source documents, CRFs, and laboratory reports. The study site will enter subject source data into the case report form. Safety laboratory data will be transferred electronically from Covance Central Laboratory Services, Inc. and Medpace Reference Laboratories to Ionis Pharmaceuticals, Inc. ECG data will be transferred electronically from BioClinica, Inc. to Ionis Pharmaceuticals, Inc. Cognitive and Neuropsychiatric scale data will be transferred electronically from MedAvante, Inc. to Ionis Pharmaceuticals, Inc. The exploratory image analysis data will be transferred electronically from Invicro, a Konica Minolta Company to Ionis Pharmaceuticals, Inc. The exploratory biomarker data will be transferred electronically from both Covance Central Laboratory Services, Inc. and Immunologix Laboratories to Ionis Pharmaceuticals, Inc.

2.2 Randomization & Treatment Allocation

In the MAD, Part 1, of the study, a patient will be randomized after all Screening assessments have been completed and after the Investigator has verified that the patient is eligible per criteria. No patient may begin treatment prior to randomization and assignment of a unique patient identification number.

Eligible patients will be randomized centrally by an automated system to receive ISIS 814907 or placebo. Within each cohort, randomization will be 3:1 ISIS 814907: placebo as outlined in Section 1.1.

The Sponsor or designee will prepare the randomization list.

In the LTE, Part 2, of the study, patients in Cohorts A and B will be registered after all Registration visit assessments for Part 2 have been completed and the Investigator has verified that the patient is eligible per criteria. Patients in Cohort C and D will transition seamlessly based

on the Part 1 eligibility criteria and do not need to be reassessed prior to the start of Part 2. In the LTE, Part 2, all eligible patients will be enrolled by an automated system to receive ISIS 814907. Patients will retain their patient identification number assigned in Part 1.

2.3 Conduct

The study will be conducted in accordance with current Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines, the World Medical Association Declaration of Helsinki guidelines, the Food and Drug Administration (FDA) Code of Federal Regulations, and all other local regulatory requirements.

2.4 Data Monitoring

2.4.1 Safety Data Monitoring

Ionis Pharmaceuticals, Inc. (or designee) is responsible for processing all reported adverse events (AEs). All serious adverse events (SAEs), reported to Ionis Pharmaceuticals, Inc. (or designee), are reviewed per standard operating procedures. The medical monitor will review all AEs and SAEs on an ongoing basis throughout the study. Ionis Pharmaceuticals, Inc. (or designee) will prepare and submit safety reports to the health authorities worldwide in accordance with local requirements. If it becomes necessary to communicate new safety information, Ionis Pharmaceuticals, Inc. (or designee) will also prepare a safety notification letter and transmit it to the study sites.

2.5 Data Management

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this Study.

2.5.1 Case Report Form (CRF) Data

BioClinica (or designee) is responsible for creating the Electronic Data Capture (EDC) data entry screens, database and edit checks using definitions developed by Ionis Pharmaceuticals, Inc. Trennic Data Services has been contracted by Ionis Pharmaceuticals, Inc. and is responsible for the review, data management querying and locking of the database.

Data are single-entered into the EDC system by the clinical site staff. Programmed edit checks (computer logic that checks the validity of the data entered and prompts for missing data that is expected to be entered) are run and automatic queries are generated. Trennic Data Services reviews all data for accuracy and validity and generates additional queries in the EDC system when necessary. The data are corrected or an explanation concerning the query is provided in the EDC system. After all data are entered, reviewed (by Data Management and Clinical Development) and queried, and all queries resolved, the database is locked.

2.5.2 Laboratory Data

Ionis Pharmaceuticals, Inc. is responsible for the format of the laboratory electronic data transfers, transfer schedule and review of the clinical laboratory data. The safety laboratory data will be provided by Covance Central Laboratory Services, Inc. and Medpace Reference Laboratories, and stored as SAS data sets or Excel files. The exploratory CSF biomarker data will be transferred electronically from both Covance Central Laboratory Services, Inc. and Immunologix Laboratories to Ionis Pharmaceuticals, Inc. Data will be provided as SAS datasets.

2.5.3 Pharmacokinetics (PK) Data

Ionis Pharmaceuticals, Inc. is responsible for the management and review of the plasma, urine drug concentration data. This process involves reviewing the patient and visit identifiers (i.e., patient demographics) with the clinical data collected in the EDC system. The PK data are not stored in the EDC system.

2.5.4 Cognitive and Neuropsychiatric Data

MedAvante (or designee) is responsible for collecting and providing external cognitive and neuropsychiatric scale data to Ionis Pharmaceuticals, Inc. External scale datasets include Geriatric Depression Rating Scale (GDS) dataset, Modified Hachinski Ischemic Scale (MHIS) dataset, Mini-Mental State Examination (MMSE) dataset, Clinical Dementia Rating (CDR) dataset, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) dataset, Neuropsychiatric Inventory Questionnaire (NPI-Q) dataset, Functional Assessment Questionnaire (FAQ) dataset, Columbia Suicide Severity Rating Scale (C-SSRS) dataset. Data will be provided as SAS datasets provided via SAS transport files.

2.5.5 Exploratory Neuroimaging Data

Invicro (or designee) is responsible for transferring the exploratory image analysis data to Ionis Pharmaceuticals, Inc. The datasets include volumetric MRI analysis dataset, FDG-PET and Tau-PET quantitative analysis dataset, cortical thickness analysis dataset, white matter lesion volume analysis dataset, CSF space analysis dataset, diffusion analysis dataset and perfusion analysis dataset. The final file structure will be comma separated value (.csv) files.

3. ANALYTICAL PLAN

3.1 General Overview of Analyses

Descriptive summary statistics including number of patients, mean, median, standard deviation, standard error of mean, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data. Where appropriate, p-values will be reported. All

statistical tests will be conducted using 2-sided tests with 5% Type I error rate unless otherwise stated.

PK parameters will be summarized by treatment group including number of patients, mean, standard deviation, coefficient of variation (CV), geometric mean, median, minimum, and maximum.

All eCRF data and data transfers from external vendors (e.g., laboratory, cognitive and neuropsychiatric testing) will be provided in the subject data listings. Patient data listings will be presented for all patients enrolled into the study.

Within this document, the terms 'patient' and 'subject' are both used to describe the individual who enrolls in this study. The terms 'MAD' and 'Part 1' may be used interchangeably. Similarly, the terms 'LTE' and 'Part 2' may be used interchangeably.

3.2 Analysis Periods, Analysis Groups, and Baseline definitions

The Analysis Periods, Analysis Groups (i.e. treatment groups), and Baseline definitions are given in the following sections. Please refer to Table B1, Table B2 and Table B3 in Appendix for more details.

3.2.1 Analysis Periods

There are four periods which will be used for analysis and are defined as:

- MAD Period: Analyses include data from MAD, Part 1.
- LTE Period: Analyses include data from LTE, Part 2.
- MAD+LTE Period: Analyses include integrated data from both MAD, Part 1 and LTE, Part 2, regardless of a subject's randomization assignment or LTE enrollment status. For example, a subject receiving MAD placebo treatment who does not enroll in LTE will still contribute data from the MAD to this analysis.
- Active Treatment Period: Analyses include data from study periods in which a subject receives active ISIS 814907 treatment. (Note: Study periods refer to Part 1 and/or Part 2, including post-treatment follow-up but excluding any variable gaps in time between Part 1 and Part 2 for subjects in Cohorts A and B). Data collected during a placebo dosing period are not included (except relevant baseline data). Subjects who receive MAD active treatment will contribute data regardless of LTE enrollment status. Subjects who receive MAD placebo treatment will only contribute data if enrolled and dosed in the LTE.

In general, listings will be created for the MAD Period and the MAD+LTE Period.

Safety, pharmacodynamic and exploratory analyses will be conducted for the MAD Period and the LTE Period separately.

The MAD+LTE Period will be used to analyze select biomarkers, neuroimaging and key clinical assessments:

- MRI (exploratory)
- Tau-PET/FDG-PET
- CSF biomarkers including but not limited to total tau, phospho-tau and A-beta42
- MMSE
- RBANS
- CDR

The Active Treatment Period will be used to analyze select safety endpoints including:

- Laboratory assessments: Potential clinically significant laboratory abnormalities, hepatotoxicity, and shift analyses
- CSF Safety Panel
- Safety MRIs
- Incidence rates for treatment emergent adverse events (TEAEs) and serious TEAEs

3.2.2 Analysis Groups

The analysis groups are described below according to the analysis periods in which they will be used.

3.2.2.1 MAD Period

- Pooled Placebo (excluding PK analyses): Cohorts A, B, C and D placebo-treated patients
- ISIS 814907 10mg Q4W: 10 mg ISIS 814907-treated patients
- ISIS 814907 30mg Q4W: 30 mg ISIS 814907-treated patients
- ISIS 814907 60mg Q4W: 60 mg ISIS 814907-treated patients
- ISIS 814907 115mg Q12W: 115 mg ISIS 814907-treated patients
- Total Active ISIS 814907 (excluding PK analyses): Cohorts A, B, C and D ISIS 814907-treated patients

3.2.2.2 LTE Period, MAD+LTE Period, and Active Treatment Period

The following analysis groups will be used for the LTE Period, MAD+LTE Period, and Active Treatment Period unless otherwise indicated. In case of very few subjects in any group, the analysis groups may be further pooled.

- Late Start A+B+C: MAD Cohorts A, B and C placebo-treated patients
- Late Start D: MAD Cohort D placebo-treated patients
- Early Start A: MAD Cohort A ISIS 814907-treated patients
- Early Start B: MAD Cohort B ISIS 814907-treated patients
- Early Start C: MAD Cohort C ISIS 814907-treated patients

- Early Start D: MAD Cohort D ISIS 814907-treated patients
- ISIS 814907 60 mg Q12W (LTE Period and Active Treatment Period):
  - LTE Period: All MAD Cohort A, B, and C roll-over subjects, regardless of randomization assignment. This group will be included for select analyses only in the LTE Period, e.g., AE and SAEs, safety analyses (except shift analyses for laboratory assessments), selected exploratory analyses only (including MRI volumetric, PET and clinical evaluations), PD and PK analyses.
  - Active Treatment Period: All MAD Cohort A, B, and C subjects, regardless of either randomization assignment or LTE enrollment status. This group will be included for select analyses only in the Active Treatment Period, e.g., serious TEAEs potentially related to Study Drug, overall summary of TEAEs, and safety MRIs.
- All Roll-over (LTE Period only, excluding PK analyses): All MAD Cohorts ISIS 814907-treated and placebo-treated roll-over patients.
- ISIS 814907 115 mg Q12W (LTE Period and Active Treatment Period): All MAD Cohort D roll-over subjects, regardless of randomization assignment (LTE Period). All MAD Cohort D subjects, regardless of either randomization assignment or LTE enrollment status (Active Treatment Period).
- Total Active (Active Treatment Period only, excluding PK analyses): All patients who receive at least 1 dose of ISIS 814907 in either the MAD or LTE periods.

In general, Early Start corresponds to a randomization assignment of active ISIS 804907 treatment in the MAD, whereas Late Start corresponds to a randomization assignment of Placebo in the MAD. The subjects and data which contribute to the analysis for a given population will be uniquely determined by both the Analysis period and Analysis group. For example, Early Start in the LTE Period includes data from subjects in the population randomized to active treatment during MAD who also enroll in the LTE; however Early Start in the MAD+LTE Period includes data from subjects in the population randomized to active treatment during MAD regardless of enrollment in the LTE.

3.2.3 Baseline definitions

3.2.3.1 MAD baseline

MAD baseline will be used for the MAD and MAD+LTE analysis periods. It is defined as the last non-missing measure prior to the first dose of study drug in the MAD, except in the instances given below:

- For vital signs (blood pressure [BP] and heart rate [HR]), baseline will be defined as the average of the triplicate values collected on Day 1 pre-dose in the MAD. If only one or two assessments are available, the single assessment or average of the two assessments will be used.

- For ECG continuous parameters, baseline will be defined as the average of the triplicate values collected on Day -1 of the MAD. If only one or two assessments are available, the single assessment or average of the two assessments will be used. For ECG interpretation, baseline will be defined as the worst categorical results of the triplicate results collected on Day -1 of the MAD.
- For PD biomarkers, baseline will be defined as the average of the Screening and Day 1 pre-dose values in the MAD.
- For C-SSRS suicidal ideation score, baseline will be defined as the maximum score collected on Day -1 and Day 1 pre-dose in the MAD.

3.2.3.2 Active treatment period baseline

Active treatment period baseline will be used to analyze the LTE Period and the Active Treatment Period. Active treatment period baseline is the same as the MAD baseline for early start subjects, and for late start subjects is the last non-missing measure collected prior to the first dose of study drug in the LTE except in the instances below:

- For vital signs (blood pressure [BP] and heart rate [HR]), as the average of the triplicate values collected on Day 1 pre-dose in the LTE. If only one or two assessments are available, the single assessment or average of the two assessments will be used.
- For ECG continuous parameters, as the average of the triplicate values collected immediately prior to first dose in the LTE. For ECG interpretation, baseline will be defined as the worst categorical results of the triplicate results collected immediately prior to first dose in the LTE.
- For C-SSRS suicidal ideation score, as the maximum score collected on Day -1 and Day 1 pre-dose in the LTE.

3.2.4 Analytical visits

All post-baseline data will be summarized using the visit labels provided in the data. Multiple results with the same visit label will be averaged for the continuous variables, and the worst result will be used for the categorical variables. Results with visit labels as “Unscheduled” will be presented in data listing, but not be included in the by-visit summary tables and figures, except for determining baseline.

3.3 Sample Size Considerations

While there is no statistical rationale for the sample size, it has been selected based on prior experience with generation 2.0 ASOs (Tabrizi et. al, 2019) given by IT bolus injection to ensure that the safety, tolerability, PKs, and exploratory pharmacodynamics will be adequately assessed while minimizing unnecessary patient exposure.

3.4 Statistical Methods

3.4.1 Patient Population Analyzed

The following analysis populations are defined for this study:

- ITT Population: All patients who are randomized and receive at least 1 dose of Study Drug (ISIS 814907 or placebo).
- Safety Population: All patients who are randomized and receive at least 1 dose of Study Drug (ISIS 814907 or placebo).
- PK Population: All patients who are randomized, receive at least 1 dose of ISIS 814907 and have sufficient sampling (at least one evaluable post-baseline PK sample) to permit PK evaluation.

The ITT population will be used for all demographic, baseline characteristics, PD and exploratory analyses. The safety population will be used for all safety analyses. PK population will be used for PK analyses.

A Per Protocol population may be considered for select analyses if necessary.

As previously indicated, the population will be used in conjunction with the analysis periods and analysis groups to uniquely indicate the subjects and data contributing to the analyses. For example, an analysis of the safety population in the Active Treatment Period for late start subjects will include data from the LTE period for subjects who were randomized and received at least one dose of study drug.

3.4.2 Handling of Missing Data

Unless otherwise specified, missing values will not be imputed.

3.4.3 Planned Interim Analysis

3.4.3.1 End of MAD, Part 1

An interim analysis of the MAD Period to investigate safety, PK, PD and exploratory endpoints will be conducted at the end of MAD, Part 1 when the last patient completes the last visit, and the results will be summarized by treatment group. Unblinded data will be evaluated at this analysis. All patients/all data through the end of MAD, Part 1 will be used for the analysis with the exception of CSF biomarkers data (through Day 1 pre-dose in LTE, Part 2). The individuals involved in the unblinded interim analysis will be identified and documented at the time of unblinded interim analysis according to Ionis standard operation procedure (SOP). The investigators, patients and study center personnel, including the site pharmacist, will be blinded to treatment assignment from the MAD for the duration of the study (i.e., until the end of LTE).

The MAD Period will be analyzed during this IA. The analysis of the LTE, MAD+LTE, and Active Treatment Periods will be performed following the final study lock after completion of the LTE period.

3.4.3.2 Safety monitoring review

A formal safety monitoring group (FSMG) will be assembled to review unblinded safety, tolerability, PK, and target engagement/PD (as needed) data collected during this study. The FSMG group is comprised of at least three medical doctors, all experienced in the conduct of clinical studies in patients with neurodegenerative diseases and otherwise independent from the conduct of the study. Unblinded statisticians or designees who will not be involved in the study conduct will generate and distribute the data to the FSMG prior to each meeting. Based on its ongoing assessment of the study data, the FSMG will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the assessments, frequency of review, meeting schedules and controlled access to unblinded data will be outlined in the FSMG charter.

3.4.4 Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized using descriptive statistics by analysis group based on the ITT population for the MAD, LTE and Active Treatment Periods separately.

Demographics include age, gender, ethnicity, race, education level in ISCED, weight, height, BMI. Height was measured at MAD Screening only, at other visits other than Screening, BMI (kg/m^2) could be computed using the formula:

$$\text{BMI} = (\text{weight in kilograms}) / [\text{height in cm} / 100]^2.$$

Baseline characteristics include individual patient CSF volume (spinal CSF volume, cranial CSF volume, and total CSF volume) and brain volumes (whole brain, ventricular, left and right hippocampal volumes), ARWMC total score; C-SSRS suicidal ideation score and clinical assessment scales (RBANS, MMSE, FAQ, NPI-Q, MHIS, CDR global and memory score, CDR Sum of Boxes, GDS-SF); CSF AD biomarkers (total tau, phospho-tau, A-beta42), CSF NfL & total NfH; prior and concomitant anti-dementia medication (cholinesterase inhibitors and memantine), estrogen replacement therapy, low dose antipsychotic medication, aspirin, fish-oil; and genetic profile (APOE, CD33, BCHE, H1 MAPT haplotype).

3.4.5 Disposition of Subjects

Patient enrollment and disposition for the MAD and LTE Periods will be summarized for each treatment group, and for all patients. By-subject disposition listings for all randomized subjects and for screen failures will also be provided for the MAD and MAD+LTE Periods.

- The summaries for the MAD Period will include: the total number of screened patients, the number of patients screen failures, the number and percentage of randomized patients, the number and percentage of patients in each analysis population the number and percentage of patients who completed the study treatment, the number and percentage of patients who terminated treatment and reason, the number and percentage of patients who completed post-treatment follow-up, and the number and percentage of patients who terminated post-treatment follow-up and reason.
- The summaries for the LTE Period will include: the number of patients that transitioned into the LTE (i.e., total number, and breakdown of number of patients by MAD dose cohort), the number of patients that did not transition into the LTE and reason, the number of patients who were registration screen failures and reason for Cohorts A and B, the number and percentage of patients in each analysis population, the number and percentage of patients completed the study treatment, the number and percentage of patients who terminated treatment and reason, the number and percentage of patients completed post-treatment follow-up, and the number and percentage of patients terminated post-treatment follow-up and reason.

Study terminations and LTE registration screen failures that are due to COVID-19 related impact will be included in the above-mentioned summary tables and subject listings.

3.4.6 Protocol Deviations

Protocol deviations will be classified to major or minor based on the study protocol deviation process plan. Protocol deviations will be provided in the data listings. Additional table may be provided to summarize the protocol deviations related to COVID-19.

A listing of all patients affected by the COVID-19 related study disruption by subject number identifier and by investigational site, and a description of how the individual's participation was altered will be provided.

Listing of medical history will be provided.

Subject listings will be performed for the MAD and MAD+LTE Periods.

3.5 Safety Analyses

The safety analyses for the MAD Period, the LTE Period, and the Active Treatment Period will be conducted on the Safety Population.

3.5.1 Exposure

Treatment duration, total amount of study drug (MAD: ISIS 814907 or placebo; LTE and Active Treatment periods: ISIS 814907) received (mg), and number of doses administered will be summarized by analysis group for the MAD, LTE, and Active Treatment Periods.

The treatment duration (days) for each subject is defined as:

- MAD Period, LTE Period separately: last dose date within the Period – first dose date within the Period + 1
- Active Treatment Period, early starters: [(last dose date in MAD – first dose date in MAD + 1) + (last dose date in LTE – first dose date in LTE + 1)]. For subjects not enrolled in LTE then it is the same as the MAD Period exposure
- Active Treatment Period, late starters: (last dose date in LTE – first dose date in LTE + 1).

3.5.2 Time on Study Analysis

The time on study analysis described below will be included in the final analysis only.

Time on study (years) will be summarized by analysis group for the MAD, LTE, MAD+LTE and Active Treatment Periods using descriptive statistics. Total time on study (patient-years) in each analysis group will be included in the summaries.

Additionally for the MAD+LTE Period, time from last dose date in MAD to first dose date in LTE (years), and time from last study visit date in MAD to first dose in LTE (days and years, separately) will be summarized by analysis group using descriptive statistics.

Time on study (days) for each subject is defined as:

- MAD Period, LTE Period separately: last study visit date within the Period – first dose date within the Period + 1
- Active Treatment Period, early starters: (last study visit date in MAD - first dose date in MAD + 1) + (last study visit date in LTE – first dose date in LTE + 1). For subjects not enrolled in LTE then it is the same as the MAD Period time on study.
- Active Treatment Period, late starters: last study visit date in LTE - first dose date in LTE + 1.
- MAD+LTE Period: (last study visit date in MAD – first dose date in MAD + 1) + (last study visit date in LTE – first dose date in LTE + 1). For subjects not enrolled in LTE then it is the same as the MAD Period time on study.

Time on study (years) for each subject is calculated as the time on study (days) divided by 365.25. Total time on study (patient-years) is calculated as the sum of time on study (years) across subjects within the analysis group and period.

For the MAD+LTE Period: Time from last dose date in MAD to first dose date in LTE (years) is defined as: (first dose date in LTE – last dose date in MAD + 1)/365.25. Time from last study visit date in MAD to first dose in LTE (days) is defined as: first dose in LTE – last study visit

date in MAD + 1; Time from last study visit date in MAD to first dose in LTE (years) is: (first dose in LTE – last study visit date in MAD + 1)/365.25.

3.5.3 Adverse Events

3.5.3.1 MAD Period and LTE Period

The incidence (proportion) of treatment-emergent adverse events (TEAEs) will be summarized for the MAD and LTE Periods separately, and incidence (rates) of TEAEs will be summarized for the Active Treatment period where indicated by *. The Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 will be used. Summaries will be presented by preferred term (PT) and system organ class (SOC), unless otherwise indicated, for:

- Any TEAE* (summarized by PT only and by both SOC and PT)
- TEAEs potentially related to Study Drug. Related is defined as “Related”, “Possible”, or missing relationship to study drug, as determined by the investigator
- TEAEs potentially related to Lumbar Puncture (LP) procedure. Related is defined as “Related”, “Possible”, or missing relationship to LP procedure
- Any TEAE by severity*. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported one or more events. TEAEs with missing severity will be categorized as “Missing” for this summary
- TEAEs potentially related to Study Drug by severity
- TEAEs potentially related to LP procedure by severity
- Serious TEAEs* (by PT only and by both SOC and PT)
- Serious TEAEs potentially related to Study Drug*
- Serious TEAEs potentially related to LP procedure*
- TEAEs leading to permanent study drug discontinuation* (by PT only and by both SOC and PT)

The number and proportion of LPs leading to TEAEs will be summarized for the MAD and LTE Periods separately. The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010. SAEs and non-serious AEs that lead to permanent study drug discontinuation will be listed separately. Non-treatment emergent adverse event will be flagged in the data listing.

An adverse event will be regarded as treatment emergent if it is present prior to receiving the first dose of study drug (MAD: ISIS 814907 or placebo; LTE and Active Treatment Periods: ISIS 814907) and subsequently worsened, or is not present prior to receiving the first dose of

study drug (MAD: ISIS 814907 or placebo; LTE and Active Treatment Periods: ISIS 814907) but subsequently appeared.

If there is no "Formlink" link, and the AE (start date/time) occurs after the subject's first dosing date/time, then the AE is treatment-emergent. Otherwise, if the AE (start date/time) occurs prior to the subject's first dosing date/time, then the AE is not treatment-emergent.

If there is a "Formlink" link between two AE records, then we compare them pairwise, and consider two cases, where we compare the AE severity (mild/moderate/severe) between the two records in the pair. We chronologically order the 2 records (by AE start date) and refer to the "first" and "second" AEs.

Case 1: The first AE record in the pair occurs before first dosing, and the second AE record occurs after first dosing.

If the AE severity or seriousness of the second record is worse than that of the first record, then only the second AE is deemed as TEAE. Otherwise, neither record is considered as TEAE.

Case 2: Both AE records in the pair occur after first dosing.

The worst AE will be deemed as a TEAE.

All TEAEs identified based on the rules above will be summarized in the event number analysis.

The most conservative approach will be used to determine if the event occurs after the treatment. For example, if the onset date or resolution date of an AE is prior to the first study treatment date, it will be considered to have occurred prior to the study period. If the onset or resolution date of an AE is a partial date with only month or year available or completely missing, then the event is assumed to be within the study period unless the year is prior to the year of the first study treatment date, or if in the same year, the month is prior to the month of the first study treatment date.

3.5.3.2 Incident rates calculation for Active Treatment Period

Incidence rates of AEs which adjust for patient-years on study will be summarized for the Active Treatment Period as indicated previously. The total time on study (patient-years) will be calculated as described in Section 3.5.2. Incidence per 100 patient-years on study will be presented, defined as: [Number of subjects reporting at least one AE during the period / Total time on study (patient-years)] × 100.

3.5.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded using WHO Drug dictionary (WHO-DD, Version SEP 2017) and summarized by ATC class, generic name/preferred medical name and by treatment group for the MAD Period and LTE Period separately.

A concomitant medication is defined as medications that were taken on or after the first day of study drug administration within the analysis period. This includes medications that were started prior to the initiation of study drug if their use continued on or after the date of the first dosing. In order to define concomitant medications with missing start or stop dates, the following additional criteria will be used:

- if both the start and stop dates of a particular medication were missing, that medication is considered concomitant;
- if the start date of a medication was missing and the stop date of that medication fell on or after the date of dosing, that medication is considered concomitant;
- if the start date of a medication was prior to the date of first dosing and the stop date of that medication was missing, that medication is considered concomitant; or
- if the start/stop date of a medication is partial then where it is not possible to rule out that it was not taken concomitantly it will be considered concomitant.

Non concomitant medications will be flagged in the data listing.

3.5.5 Columbia Suicide Severity Rating Scale (C-SSRS)

Per study design, the C-SSRS assessments will be scheduled in Part 1 and Part 2.

The C-SSRS collects binary Yes/No responses to 11 categories: five subtypes of suicidal ideation and five subtypes of suicidal behavior, and self-injurious behavior without suicidal intent. Specifically, the following outcomes are C-SSRS categories and have binary (Yes/No) responses. (The categories have been re-ordered from the actual scale to facilitate the definitions of the composite endpoints and to enable clarity in the presentation of the results (Nilsson et. al, 2013).

Suicidal Ideation:

Category 1 – Wish to Be Dead

Category 2 – Non-specific Active Suicidal Thoughts

Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act

Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan

Category 5 – Active Suicidal Ideation with Specific Plan and Intent

Suicidal Behavior:

Category 6 – Preparatory Acts or Behavior

Category 7 – Aborted Attempt

Category 8 – Interrupted Attempt

Category 9 – Actual Attempt (non-fatal)

Category 10 – Completed Suicide

Other:

Category 11 – Non-suicidal Self-Injurious Behavior

A numerical score, the Suicidal Ideation Score, will be defined as the highest suicide ideation category (1–5) at which the patient responded "Yes" for the given visit. If the patient did not respond "Yes" to any of these categories, the score will be set to zero. The baseline suicidal ideation score will be summarized as baseline characteristics.

The C-SSRS will be analyzed for the MAD Period and LTE Period separately. For each of the categories above, the number and percent of patients with a "Yes" response at any time post-baseline (regardless of baseline response) will be summarized by treatment group. C-SSRS results will be listed for the MAD and MAD+LTE Periods. All data from patients with a "Yes" response at any time post baseline will be listed separately.

3.5.6 Laboratory Measurements

The following is the list of lab analytes that will be measured throughout the study:

- Chemistry: Sodium, Potassium, Chloride, Total protein, Albumin, Calcium, Magnesium, Phosphorus, Bicarbonate, Glucose, BUN, Creatinine, Total serum Bilirubin, Uric acid, Alkaline phosphatase, AST (SGOT), ALT (SGPT), GGT and CPK.
- Hematology: Red blood cells, Hemoglobin, Hematocrit, Platelets, MCV, MCH, MCHC, White blood cells (WBC), and WBC Differential (percentage and absolute count) (Neutrophils, Eosinophils, Basophils, Lymphocytes and Monocytes)
- Coagulation: aPTT, PT, INR
- Thyroid Panel: TSH, Free T4, and Free T3
- PK: Plasma and CSF ISIS 814907 levels
- CSF Safety Panel (Minimum Requirements): Red blood cells, WBC, Glucose, Protein and Albumin
- Urinalysis: Specific gravity, pH, Protein, Glucose, Ketones, Urobilinogen, Leukocyte esterase, Nitrite, Bilirubin, Blood, Red blood cells, WBC, Epithelial cells, Bacteria, Casts, Crystals, Color and Appearance and P/C ratio
- Additional Safety Tests (plasma): Immunogenicity. (Note: samples have been collected but will not be analyzed.)

In addition:

- Plasma/serum tests measured at screening in Part 1 of the study only: Hepatitis B surface antigen, Hepatitis C antibody, HIV antibody, FSH (women only), Drug/Alcohol Screen, serum folate, serum B12, serum homocysteine, serum uric acid, Treponemal antibody
- CSF tests measured at screening in Part 1 of the study only: CSF homocysteine, folate, B12

Genetic testing is performed at Day -1 in Part 1 of the study will include: *APOE*, *BCHE*, *IL1RAP*, *CD33, H1 MAPT haplotype*, *APP*, *PSEN1*, *PSEN2*.

Missing WBC differential absolute counts and percentages will be derived as below:

If WBC differential absolute counts are missing, and percentages are available, then absolute counts will be calculated by multiplying the percentage by total WBC count. Conversely, if absolute count is available, and percentage is missing, then percentage will be calculated by dividing absolute count by the total WBC count. If neutrophils counts and percentages are missing, and segmented neutrophil and band neutrophil results are available, then neutrophils will be calculated by adding segmented neutrophils and band neutrophils.

Laboratory tests to ensure patient safety include clinical chemistry panel, hematology panel, coagulation, urinalysis and safety CSF labs (Red blood cells, WBC, Glucose, and Protein), will be summarized by treatment group and each post-baseline visit for the MAD and LTE Periods separately. These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

In addition, shift tables will be done for the MAD, LTE, and Active Treatment periods. The shifts (relative to the normal range) from baseline to the minimum and maximum post-baseline values, or shifts to abnormal, as appropriate, for each specific laboratory parameter in the following categories: CSF safety panel, coagulation, hematology, chemistry, and urinalysis (excluding microscopic examination) will be presented. If a subject is missing a baseline value but had a post-baseline value, then the baseline assessment is labeled as “unknown”. Likewise, if a subject had a baseline value but had no post-baseline values, then the minimum and maximum are labeled as “unknown”. For each parameter, the incidence of shift to low will be summarized using the minimum post-baseline values; the incidence of shift to high will be summarized using the maximum post-baseline values.

Only central laboratory data will be used for the summary tables and figures. Local laboratory data will be provided in the listings only, except for local results for CSF safety tests which will be listed and summarized in tables.

Individual data listings of all laboratory results for MAD Period and MAD+LTE Period will be presented for each subject. All values outside the clinical reference ranges will be flagged in the data listings. The abnormal value is defined as the value below the lower limit or above the upper limit of the clinical reference range. Abnormal laboratory results for the MAD and MAD+LTE Periods will also be displayed in separate listings.

3.5.6.1 Potential clinically significant laboratory abnormalities

For hematology, blood chemistry and urinalysis, the number of subjects with potentially clinically significant (PCS) laboratory abnormalities post-baseline will be summarized for the parameters provided in Table 1 for the MAD, LTE, and Active Treatment analysis periods.

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.

For the LTE and the Active Treatment period analyses, the active treatment period baseline will be used. For early start subjects, PCS abnormalities that occurred in either MAD or LTE will be included in the active treatment period analysis, whereas PCS abnormalities that occurred in the LTE will be included in the LTE analysis. For late start subjects, PCS abnormalities that occurred in the LTE period will be included.

Table 1: Clinical laboratory outlier criteria

Parameter name	PCS Low	PCS High
HEMATOLOGY		
White blood cells (Leucocytes)	<3.0 x 10^9/L	>16 x 10^9/L
Absolute Lymphocyte Count	<0.8 x 10^9/L	>12 x 10^9/L
Absolute Neutrophil Count	<1.5 x 10^9/L	>13.5 x 10^9/L
Absolute Monocyte Count	N/A	>2.5 x 10^9/L
Absolute Eosinophil Count	N/A	>1.6 x 10^9/L
Absolute Basophil Count	N/A	>1.6 x 10^9/L
Red blood cell (Erythrocyte) Count	≤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	≤0.32 L/L	≥0.54 L/L
Hematocrit - Males	≤0.37 L/L	≥0.60 L/L
Platelets	≤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
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
Creatine Kinase	N/A	≥1000 IU/L
URINALYSIS		
Glucose	N/A	≥ 1000 mg/dL; 4+
Protein	N/A	≥ 100 mg/dL; 2+ or higher

Note: ULN = upper limit of normal
The clinical laboratory outlier criteria are shown in SI units in this table.

3.5.6.2 Potential serious hepatotoxicity

Potential serious hepatotoxicity will be analyzed for the MAD, LTE, and Active Treatment Period. Potential serious hepatotoxicity is defined as a confirmed ALT or AST > 3x ULN and confirmed total bilirubin > 2x ULN at any time post-baseline in the analysis period, 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 spaghetti plot of ALT, AST, ALP 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.

A confirmed value is based on a consecutive lab value performed on a different day to, but within 7 days of, the initial value. If the consecutive value is in the same or worse ULN criteria described above, then the initial value is confirmed. If there is no retest within 7 days, then the initial value is presumed confirmed. If there are multiple results on the same day (no matter from the same lab vendor or different lab vendors), then the worst value will be utilized in the analysis.

3.5.7 Vital Signs Measurements

Vital signs will include heart rate, respiratory rate, body temperature, body weight, seated and standing systolic and diastolic blood pressure and pulse, and orthostatic changes.

Orthostatic changes include 3 variables: change from seated systolic blood pressures to average of all available standing systolic blood pressures, change from seated diastolic blood pressure to average of all available standing diastolic blood pressure, and change from seated heart rate to average of all available standing heart rate.

Summary tables will be created for the MAD and LTE Periods separately to present the descriptive statistics for vital sign values as well as the change and percent change from baseline at each post-baseline visits.

3.5.8 12-Lead Electrocardiograms (ECG)

Safety 12 lead ECG will be performed in triplicate at the visits indicated in the protocol Schedule of Procedures. ECG data will be collected through a central reader.

The ECG data will include ventricular rate (VR), PR interval, QRS duration, QT, QTcF (QT corrected using the Fridericia's formula), and QTcB (QT corrected using the Bazett's formula).

QTcF and QTcB will be calculated based on the subject's reportable ECG data at each time point using the formula described below:

$$QTcF = QT / (RR)^{1/3}, \text{ where } RR = 60 / VR$$

$$QTcB = QT / (RR)^{1/2}, \text{ where } RR = 60 / VR$$

At Screening visit, three replicates of ECG parameters will be recorded, and the mean from all replicates will be used as the patient's reportable value at Screening visit. Only calculated QTcB and QTcF will be summarized and included in the data listing. The QTC value recorded on the CRF will not be summarized and will be excluded from the data listing.

For the continuous variables, the average of measurements at a given visit will be used for analysis. For overall interpretation, the worst categorical results of triplicate results and the associated findings will be used for analysis. Summary tables will be created for the MAD and LTE Period respectively to present the descriptive statistics of the actual values, the change and percent change from baseline at each study visit for continuous variables above; and counts and percentages at each study visit for categorical responses to overall interpretation.

Criteria for potentially clinically significant used to define post-Baseline QTcB and QTcF categorization are as follows: ≤ 450 msec, >450 msec to ≤ 480 msec, >480 msec to ≤ 500 msec and >500 msec for measured values as well as >30 msec and >60 msec for changes from Baseline. The number and percentage of subjects reporting a category will be presented by treatment group, separately for QTcB and QTcF. Subjects will be counted only once if they had more than one such event during the analysis period, so only a subject's worst post-Baseline value will be considered.

All the ECG data collected in triplicate, except the CRF QTC value, will be listed.

3.5.9 Physical and Neurological Examinations

The physical & neurological examinations for the MAD and MAD+LTE Periods will be provided in patient listings.

3.5.10 Safety Neuroimaging Assessments

MRI safety sequences (T2 FLAIR, GRE T2 star, T2 Fast Spin Echo [FSE]/Turbo Spin Echo [TSE], Diffusion Tensor Imaging [DTI]) will be performed to characterize the patients' pre-treatment and post-treatment state, at Screening and Day 169 (post-treatment period) in Part 1, and at the Registration Visit (patients who are not seamlessly transitioning only), at Day 252 (or Day 336 if not performed at Day 252) and Day 449 (post-treatment period) in Part 2.

Safety MRI will be summarized for the MAD Period, LTE Period and Active Treatment Period by analysis group. During the MAD Period, the number of subjects with an increased number of microhemorrhages at Day 169 in comparison to baseline, and the number of subjects with an increased white matter disease total score at Day 169 in comparison to baseline will be

presented. Treatment-emergent (TE) brain MRI abnormalities are those occurring at Day 169 which are new (were not present at baseline) or which are worsening (were present at baseline and have a status of 'still present and increased in size' at Day 169). The number of subjects with any TE brain MRI abnormality will be summarized, as well as those with any new TE brain abnormality, and with any worsening TE brain MRI abnormality. The number of subjects with a specific type (e.g., macrohemorrhages) of new abnormality will be presented; similarly, the number with a specific type of worsening abnormality will be presented. During the LTE Period, similar analysis will be performed by analysis group at Registration Visit Part 2, Day 252 Part 2 (or Day 336 if not performed at Day 252 Part 2), and Day 449 Part 2. During the Active Treatment Period, similar summaries will be conducted by analysis group at Day 169 Part 1, Registration Visit Part 2, Day 252 Part 2 (or Day 336 if not performed at Day 252 Part 2), and Day 449 Part 2.

Safety MRI for the MAD Period and the MAD+LTE Period will be presented in data listings.

3.6 Pharmacokinetic Analysis

CSF and Plasma samples will be collected at protocol designated times for ISIS 814907 pharmacokinetic assessments from the dose cohorts. Only concentration data from patients randomized to receive study drug (ISIS 814907) will be included in this analysis. The PK analyses will be performed for the MAD Period and LTE Period separately according to the analysis groups given in Section 3.2.2.

3.6.1 CSF Concentration Data and Pharmacokinetics

A CSF sample will be collected pre-dose on each injection day in the MAD and LTE and during post-treatment evaluation periods in the MAD and LTE for PK analyses. CSF concentrations of ISIS 814907, along with the scheduled (nominal) and actual samples times (i.e., time from IT dosing) will be listed (when applicable) for each patient, analysis group, nominal dose, and day. Differences between scheduled and actual sampling days will also be listed for all patients, as well as percent differences between actual administered dose and nominal dose.

CSF concentrations below the lower limit of quantification (LLOQ) will be indicated by "BLQ". For the purpose of calculating typical descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for CSF concentrations, all BLQ values will be set to LLOQ/2 after the first active dose and will be set to 0 prior to the first active dose. Mean CSF concentrations that are BLQ will be presented as BLQ, and the SD and %CV will be reported as not applicable. Summary statistics of the ISIS 814907 CSF concentrations will be tabulated for the MAD and LTE Periods separately by analysis group, nominal dose and day. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling days, or large deviations between actual dose and nominal dose.

The ISIS 814907 half-life in CSF will be calculated, if possible, for the MAD Period and summarized by analysis group, nominal dose, and nominal day.

ISIS 814907 CSF concentration versus time (actual) profiles from Day 1 to last collection, for each patient, as well as the mean (±SE) CSF concentration versus time (scheduled) profiles for each treatment cohort, will be presented graphically on linear scale for the MAD and LTE Periods separately. Samples may be excluded from the mean plots if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

3.6.2 Plasma Concentration Data

Plasma concentrations of ISIS 814907, along with the scheduled (nominal) and actual samples times (i.e., time from IT dosing) will be listed (when applicable) for each patient, analysis group, nominal dose, and day. Percent differences between scheduled and actual sampling times will also be listed for all patients as well as percent differences between actual administered dose and nominal dose.

Plasma concentrations below the lower limit of quantification (LLOQ) will be indicated by "BLQ". For the purpose of calculating typical descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for plasma concentrations, all BLQ values will be set to LLOQ/2 with the exception of concentration prior to the first dose which will be set to '0'. Mean plasma concentrations that are BLQ will be presented as BLQ, and the SD and %CV will be reported as not applicable. Summary statistics of the ISIS 814907 plasma concentrations will be tabulated for the MAD and LTE periods separately by analysis group, nominal dose, day, and scheduled time point. At the discretion of the pharmacokinetic scientist and/or biostatistician, samples may be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

ISIS 814907 plasma concentration versus time (actual) profiles from Day 1 (MAD and LTE Periods), Day 29 (MAD period), Day 85 up to Day 141 (MAD period), and Day 337 up to Day 421 (LTE period), for each patient, as well as the mean (±SE) plasma concentration versus time (scheduled) profiles by analysis group will be presented graphically on linear and semilogarithmic scales. Additionally, ISIS 814907 plasma concentration versus time (actual) profiles from 0 to 24 hours on Days 1 and 85 (MAD period) and Days 1 and 337 (LTE period) for all patients, as well as the mean (±SE) plasma concentration versus time (scheduled) profiles (0 to 24 hours on Days 1 and 85 [MAD period]; 0 to 24 hours on Days 1 and 337 [LTE period]) for each analysis group will be presented graphically on linear and semilogarithmic scales. Samples may be excluded from the mean plots if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

3.6.3 Plasma Pharmacokinetics

Non-compartmental pharmacokinetic analysis of ISIS 814907 will be carried out on each individual patient data set using Phoenix WinNonlin version 6.3 or higher (Pharsight Corporation, Mountain View, CA). Plasma pharmacokinetic parameters in each patient (when applicable) will be determined. For calculation of PK parameters, all BLQ values will be set to zero. The following plasma PK parameters will be calculated (when applicable) and based on actual sampling times:

Table 2: Plasma PK parameters in Part 1-MAD and Part 2-LTE

Part 1 – MAD			
Parameter	**Definition/Method**	**Day 1**	**D85**
C_{max}	Maximum observed concentration	X	X
T_{max}	Observed time at which C_{max} occurs	X	X
T_{last}	Time of last measurable (positive) concentration	X	X
$AUC_{0\text{-}24hr}$	Partial AUC: Area under the concentration-time curve from time zero to 24 hours post dose, calculated using linear-up log-down method.	X	X
$AUC_{0\text{-}28days}$	Partial AUC: Area under the concentration-time curve from time zero to 28 days), calculated using linear-up log-down method (aka, AUC_{τ})		X
$t_{1/2\lambda z}$	Terminal elimination half-life determined from the equation: ln 2/λ_z, where λ_z is the first-order rate constant associated with the terminal (log-linear) elimination phase. This is estimated via linear regression of time vs. log concentration. A minimum of three data points in the elimination phase will be used to define λ_z and the correlation of determination values (r^2) had to be at or greater than 0.8 for the estimate to be accepted.		X
CL_{ss}/F	Steady-state clearance divided by F (fraction of the dose absorbed) determined by $Dose/AUC_{0\text{-}28days}$		X
$CL_{0\text{-}24hr}/F$	Clearance after first dose divided by F (fraction of the dose absorbed) determined by $Dose/AUC_{0\text{-}24hr}$	X	
V_z/F	Volume of distribution (based on the terminal phase) divided by F (fraction of the dose absorbed)		X
Part 2 – LTE			
Parameter	**Definition/Method**	**Day 1**	**D337**
C_{max}	Maximum observed concentration	X	X
T_{max}	Observed time at which C_{max} occurs	X	X
T_{last}	Time of last measurable (positive) concentration	X	X
$AUC_{0\text{-}24hr}$	Partial AUC: Area under the concentration-time curve from time zero to 24 hours post dose, calculated using linear-up log-down method.	X	X
$AUC_{0\text{-}28days}$	Partial AUC: Area under the concentration-time curve from time zero to 28 days), calculated using linear-up log-down method (aka, AUC_{τ})		X
$t_{1/2\lambda z}$	Terminal elimination half-life determined from the equation: ln 2/λ_z, where λ_z is the first-order rate constant associated with the terminal (log-linear) elimination phase. This is estimated via linear regression of time vs. log concentration. A minimum of three data points in the elimination phase will be used to define λ_z and the correlation of determination values (r^2) had to be at or greater than 0.8 for the estimate to be accepted.		X
CL_{ss}/F	Steady-state clearance divided by F (fraction of the dose absorbed) determined by $Dose/AUC_{0\text{-}28days}$		X
$CL_{0\text{-}24hr}/F$	Clearance after first dose divided by F (fraction of the dose absorbed) determined by $Dose/AUC_{0\text{-}24hr}$	X	
V_z/F	Volume of distribution (based on the terminal phase) divided by F (fraction of the dose absorbed)		X

Plasma pharmacokinetic parameters (if applicable) will be summarized using descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) treatment cohort, nominal dose, and day.

Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

3.7 Pharmacodynamic and Exploratory Analysis

The pharmacodynamic and exploratory analyses, including evaluation of target engagement (total tau and phosphor-tau), will be conducted on the ITT population for the MAD, LTE, and MAD+LTE (where indicated) Periods.

Exploratory analyses of covariates of interest may be performed as post hoc analysis to evaluate their association with changes from baseline in neuroimaging parameters, cognitive assessments, or PK/PD and safety parameters. Covariates of interest may include, but are not limited to, demographics, medical history, concomitant medications, baseline characteristics (i.e., biomarkers, cognitive assessments, genotype and neuroimaging parameters).

3.7.1 Biochemical Analysis

Total tau in CSF is the key exploratory endpoint for the study. Other potential CSF biomarkers included in the analysis are target engagement (phospho-tau), A-beta42, A-beta40, total tau to A-beta42 ratio, A-beta42 to A-beta40 ratio, NfL, total NfH, neurogranin, YKL-40. If total tau to A-beta42 ratio is missing, but total tau and A-beta42 are available, then total tau to A-beta42 ratio will be derived as total tau divided by A-beta42. A-beta42 to A-beta40 ratio will be derived as A-beta42 divided by A-beta40.

In the MAD Period, the actual values, change, and percent change from baseline for CSF biomarkers at each visit will be summarized using descriptive statistics. CSF biomarkers at Day 1 (pre-dose) visit in the LTE will also be added in the MAD Period analysis. The absolute change and percent change from baseline for CSF biomarkers at each post-baseline visit will be compared between ISIS814907-treated groups and the pooled placebo group. The absolute changes from baseline at each post-baseline visit will be compared between each ISIS 814907 treated analysis group and pooled placebo using the ANCOVA with baseline value as covariate or Wilcoxon Rank Sum test, as appropriate. Since the percent change from baseline for biochemical data is not always normally distributed, an analysis of covariance (ANCOVA) model will be fit to the log-transformed data with treatment group as factors and log-transformed baseline value as covariate. The log-transformed data is obtained by taking the log of the ratio of post-baseline and baseline values, i.e., log (Y/X), where Y is the post-baseline value and X is the baseline value of biomarker. The model will provide an estimate of the log ratio $\hat{c}$, which will be converted back to the ratio scale. The percent change from baseline will then be estimated based

on the estimated ratio scale, that is $[\exp(\hat{c}) - 1] \times 100\%$. The results provide an overall estimate, with corresponding CIs and p-value.

The key analysis in the MAD, Part 1, of the study is the correlation of CSF trough concentration of ISIS 814907 on Day 85 with change in CSF tau concentration from baseline to final CSF collection. ISIS 814907 dose and PK (CSF trough concentration of ISIS 814907 on Day 85) will be related to target engagement using the change in CSF total tau level from baseline to Day 85 and to each CSF collection in the Post-Treatment Period. In the LTE, Part 2, of the study a key analysis will be the correlation of CSF trough concentrations of ISIS 814907 on Day 337 with change in CSF tau concentration from baseline to final CSF collection. Additional correlations between ISIS 814907 dose or PK (CSF trough concentration of ISIS 814907 on Day 85) and changes in pharmacodynamic endpoints may be produced.

In the LTE and MAD+LTE Periods, the actual values, change, and percent change from baseline for CSF biomarkers at each visit will be summarized using descriptive statistics.

Pearson correlation coefficients and related p-value will be reported in the correlation analysis. A scatterplot will be produced to display the correlation between two quantitative variables.

All evaluated parameters will be presented in data listings.

3.7.2 Neuroimaging Analysis

All MRI and PET imaging parameters will be presented in data listings for the MAD and MAD+LTE Periods, separately.

3.7.2.1 Structural MRI – Volumetric Analysis

Structural MRI analyses will be performed for the MAD, LTE, and MAD+LTE Periods.

Hippocampal volumes (left, right and total), whole brain volume, ventricular volumes (including lateral ventricle right, lateral ventricle left, 3rd ventricle, 4th ventricle, all ventricles), and baseline/screening total intracranial volume (ICV) will be assessed using MRI. The ROIs are listed in Appendix Table A1. The volumes of hippocampus, whole brain, and ventricles as a % of total intracranial volume can be calculated by: (Volume / ICV) *100. It is important to note that changes in volume may be due to atrophy or the reduction of tau neurofibrillary tangles, amyloid-beta plaques, or inflammation due to treatment (pseudo-atrophy). Volumetric analyses cannot distinguish between these possibilities.

In the MAD Period, the following results at each visit will be summarized using descriptive statistics:

- Raw results in baseline/screening Total Intracranial Volume (ICV)
- Raw results and absolute changes from baseline in whole brain volume, whole brain volume as a % of total ICV, hippocampal volumes (left, right and total), and hippocampal volumes as a % of total ICV, ventricular volumes (lateral ventricle right,

lateral ventricle left, 3rd ventricle, 4th ventricle, all ventricles), and ventricular volumes as a % of total ICV

The absolute change from baseline in whole brain volume, hippocampal volumes, ventricular volumes as listed in Table A1, and the aforementioned volumes as % of ICV will be compared between each ISIS 814907 treated analysis group and pooled placebo using the ANCOVA with baseline value and baseline age as covariates or Wilcoxon Rank Sum test, as appropriate.

In the LTE and MAD+LTE Periods, the actual values in baseline/screening ICV; the actual values and absolute changes from baseline in whole brain volume, hippocampal volumes, ventricular volumes and the aforementioned volumes as a % of total ICV will be summarized at each visit using descriptive statistics.

3.7.2.2 Exploratory MRI Analyses

3.7.2.2.1 Perfusion Analysis – Arterial spin labelling (ASL)

ASL MRI will be used to quantitate changes in tissue perfusion. The measurement of cerebral blood flow (CBF) in specific regions of interest will assess if changes have occurred between baseline and subsequent imaging timepoints. We will calculate six composites: frontal, cingulate, medial temporal, temporal, parietal, and occipital. Each composite can be derived by averaging the perfusion results from the individual regions listed in Appendix Table A2 constituting the composite.

In the MAD Period, the actual values of each composite and absolute changes from baseline at Day 169 visit will be summarized using descriptive statistics. The absolute changes from baseline at Day 169 will be compared between each ISIS 814907 treated analysis group and pooled placebo using the ANCOVA with baseline value and baseline age as covariates or Wilcoxon Rank Sum test, as appropriate. In case of very few evaluable scans, only descriptive summary by visit will be provided and ANCOVA may not be performed.

In the LTE and MAD+LTE Periods, the actual values and changes from baseline at Day 449 visit will be summarized using descriptive statistics.

3.7.2.2.2 Diffusion Analysis

To assess if the integrity of white matter (WM) is affected by the intervention, analysis of DTI scans will be performed. DTI allows for the identification of microscopic changes in WM tracts (e.g., demyelination) through assessing microscopic changes in water molecule mobility (diffusion). Measurements of water diffusion in WM includes mean, radial, and axial diffusivity and fractional anisotropy (FA). These measurements will be carried out within specific ROIs of the brain. The ROIs include cingulum and hippocampus left and right, forceps major (posterior forceps) and fornix as listed in Appendix Table A3.

In the MAD Period, the actual values and absolute changes from baseline at Day 169 visit will be summarized using descriptive statistics. The absolute changes from baseline at Day 169 will be compared between each ISIS 814907 treated analysis group and pooled placebo using the ANCOVA with baseline value and baseline age as covariates or Wilcoxon Rank Sum test, as appropriate.

In the LTE and MAD+LTE Periods, the actual values and changes from baseline at Day 449 visit will be summarized using descriptive statistics.

3.7.2.2.3 Cortical Thickness

To assess if the intervention is affecting atrophy, the average cortical thickness will be measured in regions known to be affected by AD. T1 MRI scans will be analyzed to determine average cortical thickness (mm) for the whole brain for each patient and timepoint to assess changes with treatment and time. It is important to note that changes in cortical thickness may be due to atrophy or the reduction of tau neurofibrillary tangles, amyloid-beta plaques, or inflammation due to treatment (pseudo-atrophy). Cortical thickness analyses cannot distinguish between these possibilities.

In the MAD Period, the actual values of cortical thickness and absolute changes from baseline at Day 169 visit will be summarized using descriptive statistics. The absolute changes from baseline at Day 169 will be compared between each ISIS 814907 treated analysis group and pooled placebo using the ANCOVA with baseline value and baseline age as covariates or Wilcoxon Rank Sum test, as appropriate.

In the LTE and MAD+LTE Periods, the actual values and changes from baseline at Day 449 visit will be summarized using descriptive statistics.

3.7.2.2.4 White matter lesion analysis

WM lesion analysis will measure the volume of white matter lesions relative to treatment and timepoint. A Lesion Prediction Algorithm (LPA) (Schmit P., 2016) will be implemented to estimate the white matter lesion (WML) volume.

In the MAD Period, the actual values of WML volume and absolute changes from baseline at Day 169 visit will be summarized using descriptive statistics. The absolute changes from baseline at Day 169 will be compared between each ISIS 814907 treated analysis group and pooled placebo using the ANCOVA with baseline value and baseline age as covariates or Wilcoxon Rank Sum test, as appropriate.

In the LTE and MAD+LTE Periods, the actual values and changes from baseline at Day 449 visit will be summarized using descriptive statistics.

3.7.2.2.5 CSF space analysis

The CSF space in individuals will be assessed on T1 and T2 MRI of the brain and spinal cord at screening only. Total CSF space varies between individuals, and atrophy further increases the variability. Assessment of CSF will be determined for each patient on screening MRIs (Chazen et. al, 2017; De Leener et. al, 2018; Sandhya et. al, 2017). Total CSF includes both cranial CSF and spinal CSF. Thus, the total CSF volume is calculated by adding the cranial and spinal CSF volumes. The imaging of CSF space at Screening will be summarized as baseline characteristics.

3.7.2.3 Positron emission tomography (PET) Analysis

This analysis will be performed on the ITT population for the MAD, LTE, and MAD+LTE Periods.

Patients will undergo FDG-PET or Tau-PET imaging to visualize brain changes. In the MAD Period, PET imaging will only be done in Cohorts C and D, and in the LTE, PET imaging will be done in all patients.

- For Cohorts C and D, PET imaging will be done 3 times over the course of the study: during the MAD screening window, at the MAD Day 169 visit, and at the Day 449 visit in the LTE.
- For patients from Cohorts A and B returning to participate in the LTE, PET imaging will be at 2 time points, during the LTE Registration Period and at the Day 449 visit in the LTE.

If Tau-PET is either not available at the site or has not yet been approved, then FDG-PET should be performed. If Tau-PET becomes available to patients in Cohorts C and D in the MAD, then patients should switch to Tau-PET if there are at least 2 imaging time points remaining to enable longitudinal analyses.

Standard uptake values (SUVs) will be extracted to calculate standard uptake value ratio (SUVR), the ratio of target region SUV to reference region SUVs. SUVR values will be computed for the target ROIs. The SUVR values of ROIs will be used to calculate six composites for FDG- or Tau-PET: frontal, cingulate, medial temporal, temporal, parietal, and occipital. Each composite can be derived by averaging the SUVR values from the individual regions listed in Appendix Table A2 constituting the composite. For Tau-PET, the composites will be obtained using the SUVRs that are calculated using cerebellum ventral as the reference region. For FDG-PET, the composites will be obtained using the SUVRs that are calculated using whole cortex, pons vermis and AD preserved as reference regions, respectively.

In the MAD Period, the actual values of each composite and absolute changes from baseline at Day 169 visit will be summarized using descriptive statistics. The absolute changes from baseline at Day 169 will be compared between each ISIS 814907 treated analysis group and pooled placebo using the using the ANCOVA with baseline value as a covariate or Wilcoxon Rank Sum test, as appropriate. In case of very few evaluable scans, only descriptive summary by visit will be provided and ANCOVA may not be performed.

In the LTE Period and MAD+LTE Period, the actual values of each composite and changes from baseline at post-baseline visit will be summarized using descriptive statistics.

FDG- and Tau- PET SUVR results of the target ROIs and the composite values will be presented in data listings for the MAD and MAD+LTE Periods.

3.7.3 Clinical Evaluations

3.7.3.1 Functional Activities Questionnaire (FAQ)

FAQ is used to measure functioning/ability to perform activities of daily living.

In the MAD Period, FAQ total score (actual value, absolute change and percent change from baseline) will be summarized by treatment group and each post-baseline visit at Day 113, 169 and 253 visits using descriptive statistics. The absolute changes from baseline at each post-baseline visit will be compared between each ISIS 814907 treated analysis group and pooled placebo using the ANCOVA with baseline value as a covariate or Wilcoxon Rank Sum test, as appropriate.

In the LTE Period, the actual values, changes and percent changes from baseline at Day 449 visit will be summarized using descriptive statistics.

All FAQ collected scores will be presented in data listings for the MAD and MAD+LTE Periods.

3.7.3.2 Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The RBANS assessment yields five index scores, one for each of the domains tested: attention, visuospatial/constructional abilities, language, immediate memory and delayed memory.

In the MAD Period, RBANS index scores, sum of index scores and total scale (actual value, absolute change and percent change from baseline) will be summarized by treatment group and each post-baseline visit at Day 56, 113, 169 and 253 visits using descriptive statistics. The absolute changes from baseline at each post-baseline visit will be compared between each ISIS 814907 treated analysis group and pooled placebo using the ANCOVA with baseline value as a covariate or Wilcoxon Rank Sum test, as appropriate.

In the LTE Period and the MAD + LTE Periods, the actual values, changes and percent changes will be summarized by analysis group and each post-baseline visit within the Period.

All RBANS collected scores will be presented in data listings for the MAD and MAD+LTE Periods.

3.7.3.3 Mini-mental State Examination (MMSE)

The MMSE has five different domains:

- Orientation: a maximum of 10 points, calculated by adding Orientation to Time and Orientation to Place;
- Memory: a maximum of 6 points, calculated by adding Recall and Registration;

- Attention/Calculation: a maximum of 5 points;
- Language: a maximum of 8 points, calculated by adding Naming, Comprehension, Repetition, Reading and Writing;
- Visual construction: a maximum of 1 point, which is Drawing.

In the MAD Period, MMSE domain scores and total score (actual value, absolute change and percent change from baseline) will be summarized by treatment group and each post-baseline visit at Day 56, 113, 169 and 253 visits using descriptive statistics. The absolute changes from baseline at each post-baseline visit will be compared between each ISIS 814907 treated analysis group and pooled placebo using the ANCOVA with baseline value as a covariate or Wilcoxon Rank Sum test, as appropriate.

In the LTE and MAD+LTE Periods, the actual results, changes and percent changes will be summarized by analysis group and each post-baseline visit within the period.

All MMSE collected scores will be presented in data listings for the MAD and MAD+LTE Periods.

3.7.3.4 Neuropsychiatric Inventory - Questionnaire (NPI-Q)

The NPI-Q is an informant-based instrument that measures the presence and severity of 12 neuropsychiatric symptoms (e.g., anxiety, disinhibition, agitation/aggression). NPI-Q scores include Severity score (for patient) and Distress score (for caregiver). The severity scale has scores ranging from 1 to 3 points, and the scale for assessing caregiver distress has scores ranging from 0 to 5 points. Higher scores indicate more severity/distress. Total severity score is calculated as sum of severity scores for all 12 domains; and total distress score is calculated as sum of distress scores for all 12 domains.

In the MAD Period, the NPI-Q total severity score and total distress score (actual value, absolute change and percent change from baseline) will be summarized by treatment group and each post-baseline at Day 113, 169 and 253 visits using descriptive statistics. The absolute changes from baseline at each post-baseline visit will be compared between each ISIS 814907 treated analysis group and pooled placebo using the ANCOVA with baseline value as a covariate or Wilcoxon Rank Sum test, as appropriate.

In the LTE Period, the actual values, changes and percent changes will be summarized by analysis group and post-baseline visit at Day 449.

All NPI-Q collected scores will be presented in data listings for the MAD and MAD+LTE Periods.

3.7.3.5 Clinical Dementia Rating (CDR) Scale

The CDR is a global scale used at Screening to categorize the severity of Alzheimer's type dementia. It is used to rate the patient's cognitive performance in 6 domains: memory,

orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Categorical scores for each domain are 0 (none), 0.5 (questionable), 1 (mild), 2 (moderate) and 3 (severe). A summed total score (CDR Sum of Boxes [CDR-SOB]) is produced, and a global score (using the same 5 grades of dementia) is derived. CDR are collected at Screening (all cohorts), Registration/Part 2 (Cohorts A and B only) and Day 449/Part 2 (all cohorts).

In the MAD period, the CDR-SOB at Screening will be summarized as baseline characteristics.

In the LTE and MAD+LTE Periods, CDR-SOB, global score and subdomain scores (actual value, absolute change and percent change from baseline) will be summarized by analysis group and each post-baseline visit at Registration visit (for Cohorts A and B only) and at Day 449 visit.

All CDR collected scores will be presented in data listings for the MAD and MAD+LTE Periods.

4. REFERENCES

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5. APPENDIX

Table A1: ROIs for Volumetric Analysis

ROI Name	ROI Description
INTRACRANIAL [a]	Total Intracranial Volume (ICV)
HIPPOCAMPUS_RIGHT	Hippocampus right
HIPPOCAMPUS_LEFT	Hippocampus left
HIPPOCAMPUS [*]	Hippocampus
VENTRICLE_LATERAL_RIGHT	Lateral Ventricle right
VENTRICLE_LATERAL_LEFT	Lateral Ventricle left
THIRD_VENTRICLE	3rd Ventricle
FOURTH_VENTRICLE	4th Ventricle
BRAIN_VENTRICLE [**]	All ventricles
WHOLE_BRAIN	Whole brain

[a] ROI will only be calculated for baseline/screening scans
[*] Total Hippocampal Volume is calculated by adding up the volumes of Hippocampus right and Hippocampus left.
[**] Total Brain Ventricular Volume is calculated by adding up the volumes of Lateral Ventricle right, Lateral Ventricle left, 3rd Ventricle and 4th Ventricle.

Table A2: ROIs for Perfusion and PET Analyses

ROI Name	ROI Description	Composite
FRONTAL_LOBE_MIDDLE_L	Middle frontal gyrus left	Frontal Composite
FRONTAL_LOBE_MIDDLE_R	Middle frontal gyrus right	
FRONTAL_LOBE_PRECENTRAL_L	Precentral gyrus left	
FRONTAL_LOBE_PRECENTRAL_R	Precentral gyrus right	
FRONTAL_LOBE_STRAIGHT_GYRUS_L	Straight gyrus left	
FRONTAL_LOBE_STRAIGHT_GYRUS_R	Straight gyrus right	
ORBITOFRONTAL_CORTEX_ANTERIOR_L	Anterior orbital gyrus left	
ORBITOFRONTAL_CORTEX_ANTERIOR_R	Anterior orbital gyrus right	
FRONTAL_LOBE_INFERIOR_L	Inferior frontal gyrus left	
FRONTAL_LOBE_INFERIOR_R	Inferior frontal gyrus right	
FRONTAL_LOBE_SUPERIOR_L	Superior frontal gyrus left	
FRONTAL_LOBE_SUPERIOR_R	Superior frontal gyrus right	
ORBITOFRONTAL_CORTEX_MEDIAL_L	Medial orbital gyrus left	
ORBITOFRONTAL_CORTEX_MEDIAL_R	Medial orbital gyrus right	
ORBITOFRONTAL_CORTEX_LATERAL_L	Lateral orbital gyrus left	
ORBITOFRONTAL_CORTEX_LATERAL_R	Lateral orbital gyrus right	
ORBITOFRONTAL_CORTEX_POSTERIOR_L	Posterior orbital gyrus left	
ORBITOFRONTAL_CORTEX_POSTERIOR_R	Posterior orbital gyrus right	
CINGULATE_SUBGENUAL_ANTERIOR_L	Subgenual frontal cortex left	Cingulate Composite
CINGULATE_SUBGENUAL_ANTERIOR_R	Subgenual frontal cortex right	

SUBCALLOSAL_AREA_L	Subcallosal area left	
SUBCALLOSAL_AREA_R	Subcallosal area right	
CINGULATE_PRESUBGENUAL_ANTERIOR_L	Pre-subgenual frontal cortex left	
CINGULATE_PRESUBGENUAL_ANTERIOR_R	Pre-subgenual frontal cortex right	
CINGULATE_ANTERIOR_L	Cingulate gyrus anterior part left	
CINGULATE_ANTERIOR_R	Cingulate gyrus anterior part right	
CINGULATE_POSTERIOR_L	Gyrus cinguli posterior part left	
CINGULATE_POSTERIOR_R	Gyrus cinguli posterior part right	
HIPPOCAMPUS_L	Hippocampus left	Medial Temporal Composite
HIPPOCAMPUS_R	Hippocampus right	
TEMPORAL_LOBE_ANTERIOR_MEDIAL_L	Anterior temporal lobe medial part left	
TEMPORAL_LOBE_ANTERIOR_MEDIAL_R	Anterior temporal lobe medial part right	
TEMPORAL_LOBE_ANTERIOR_LATERAL_L	Anterior temporal lobe lateral part left	
TEMPORAL_LOBE_ANTERIOR_LATERAL_R	Anterior temporal lobe lateral part right	
PARAHIPPOCAMPAL_L	Parahippocampal and ambient gyri left	
PARAHIPPOCAMPAL_R	Parahippocampal and ambient gyri right	
TEMPORAL_LOBE_SUPERIOR_POSTERIOR_L	Superior temporal gyrus posterior part left	Temporal Composite
TEMPORAL_LOBE_SUPERIOR_POSTERIOR_R	Superior temporal gyrus posterior part right	
TEMPORAL_LOBE_MIDDLE_INFERIOR_L	Middle and inferior temporal gyrus left	
TEMPORAL_LOBE_MIDDLE_INFERIOR_R	Middle and inferior temporal gyrus right	
FUSIFORM_GYRUS_L	Fusiform gyrus left	
FUSIFORM_GYRUS_R	Fusiform gyrus right	
TEMPORAL_LOBE_POSTERIOR_L	Posterior temporal lobe left	
TEMPORAL_LOBE_POSTERIOR_R	Posterior temporal lobe right	
TEMPORAL_LOBE_SUPERIOR_ANTERIOR_L	Superior temporal gyrus anterior part left	
TEMPORAL_LOBE_SUPERIOR_ANTERIOR_R	Superior temporal gyrus anterior part right	
PARIETAL_LOBE_POSTCENTRAL_L	Postcentral gyrus left	Parietal Composite
PARIETAL_LOBE_POSTCENTRAL_R	Postcentral gyrus right	
PARIETAL_LOBE_SUPERIOR_L	Superior parietal gyrus left	
PARIETAL_LOBE_SUPERIOR_R	Superior parietal gyrus right	
PARIETAL_LOBE_INFERIORLATERAL_L	Inferiolateral remainder of parietal lobe left	
PARIETAL_LOBE_INFERIORLATERAL_R	Inferiolateral remainder of parietal lobe right	
OCCIPITAL_LOBE_LATERAL_L	Lateral remainder of occipital lobe left	Occipital Composite
OCCIPITAL_LOBE_LATERAL_R	Lateral remainder of occipital lobe right	
OCCIPITAL_LOBE_LINGUAL_GYRUS_L	Lingual gyrus left	
OCCIPITAL_LOBE_LINGUAL_GYRUS_R	Lingual gyrus right	
OCCIPITAL_LOBE_CUNEUS_L	Cuneus left	
OCCIPITAL_LOBE_CUNEUS_R	Cuneus right	

Table A3: ROIs for Diffusion Analysis

ROI Name	ROI Description
CINGULUM_HIPPOCAMPUS	Cingulum and hippocampus left and right
FORCEPS_MAJOR	Forceps major (posterior forceps)
FORNIX	Fornix

Table B1: LTE Period: Analysis Groups and Baseline Definition

Baseline reference [1]	Cohort	MAD period treatment	LTE period treatment [2]	Late start ABC	Late start D	Early start A	Early start B	Early start C	Early start D	ISIS 814907 60 mg Q12W [3]	ISIS 814907 115 mg Q12W	All Roll-over
prior to LTE	A	Placebo	ISIS 814907 60 mg q12w	X						X		X
	B	Placebo	ISIS 814907 60 mg q12w	X						X		X
	C	Placebo	ISIS 814907 60 mg q12w	X						X		X
	D	Placebo	ISIS 814907 115 mg q12w		X						X	X
prior to MAD	A	ISIS 814907 10 mg q4w	ISIS 814907 60 mg q12w			X				X		X
	B	ISIS 814907 30 mg q4w	ISIS 814907 60 mg q12w				X			X		X
	C	ISIS 814907 60 mg q4w	ISIS 814907 60 mg q12w					X		X		X
	D	ISIS 814907 115 mg q12w	ISIS 814907 115 mg q12w						X		X	X

[1] Please refer to Section 3.2.2 and 3.2.3 for details and exceptional instances.
[2] As indicated by the orange highlighting, only the LTE period (and relevant baseline) data will contribute to the analysis.
[3] Select analyses only.
Note: In case of very few subjects, the analysis groups may be pooled.

Table B2: MAD+LTE Period: Analysis Groups and Baseline Definition

Baseline reference [1]	Cohort	MAD period treatment [2]	LTE period treatment [2]	Late start ABC	Late start D	Early start A	Early start B	Early start C	Early start D
prior to MAD	A	Placebo	ISIS 814907 60 mg q12w	X					
	B	Placebo	ISIS 814907 60 mg q12w	X					
	C	Placebo	ISIS 814907 60 mg q12w	X					
	D	Placebo	ISIS 814907 115 mg q12w		X				
	A	ISIS 814907 10 mg q4w	ISIS 814907 60 mg q12w			X			
	B	ISIS 814907 30 mg q4w	ISIS 814907 60 mg q12w				X		
	C	ISIS 814907 60 mg q4w	ISIS 814907 60 mg q12w					X	
	D	ISIS 814907 115 mg q12w	ISIS 814907 115 mg q12w						X

[1] Please refer to Section 3.2.2 and 3.2.3 for details and exceptional instances.
[2] As indicated by the orange highlighting, data from both the MAD and LTE periods will contribute to the analysis.
Note: In case of very few subjects, the analysis groups may be pooled.

Table B3: Active Treatment Period: Analysis Groups and Baseline Definitions

Baseline reference [1]	Cohort	MAD period treatment [2]	LTE period treatment [2]	Late start ABC	Late start D	Early start A	Early start B	Early start C	Early start D	ISIS 814907 115mg Q12W	Total Active
prior to LTE	A	Placebo	ISIS 814907 60 mg q12w	X							X
	B	Placebo	ISIS 814907 60 mg q12w	X							X
	C	Placebo	ISIS 814907 60 mg q12w	X							X
	D	Placebo	ISIS 814907 115 mg q12w		X					X	X
prior to MAD	A	ISIS 814907 10 mg q4w	ISIS 814907 60 mg q12w			X					X
	B	ISIS 814907 30 mg q4w	ISIS 814907 60 mg q12w				X				X
	C	ISIS 814907 60 mg q4w	ISIS 814907 60 mg q12w					X			X
	D	ISIS 814907 115 mg q12w	ISIS 814907 115 mg q12w						X	X	X

[1] Please refer to Section 3.2.2 and 3.2.3 for details and exceptional instances.
[2] As indicated by the orange highlighting, data from periods in which a subject received active ISIS 814907 treatment (and relevant baseline data) will be included in the active treatment period analysis. Data collected during placebo dosing are not included (except relevant baseline data).
Note: In case of very few subjects, the analysis groups may be pooled.
Note: ISIS 814907 60 mg Q12W group will be included for select analyses only in the Active Treatment Period, including: serious TEAEs potentially related to Study Drug, overall summary of TEAEs, and safety MRIs.

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APPROVALS:

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