STATISTICAL ANALYSIS PLAN

Trial Sponsor:	Alector Inc.
Protocol Number:	AL002-LTE
IND Number:	[redacted]
EudraCT Number:	
EU CT Number:	
Investigational Drug:	AL002
Indication:	Alzheimer's Disease
Dosage Form/Strength:	IV 15 mg, 40 mg, and 60 mg/kg
Protocol Version:	2.0
Protocol Approval Date	20 January 2024

Protocol Title: A Multicenter, Long-Term Extension Study to Evaluate the Safety, Tolerability, and Efficacy of AL002 in Participants with Alzheimer's Disease

Sign-off Date:	
Version:	1.0
Last Revision Date:	25 Oct 2024
Archive Date:	

SIGN-OFF SIGNATURES

Study Biostatistician:

Michael Edwardes
[redacted]
Everest Clinical Research Corporation

Dean Rutty
25 Oct 2024 15:40:05 (-04:00)
REASON: I approve this document.
cf05f229-4a1f-4d58-ac25-8bd2e3adbcce

Signature **Date**

Dean Rutty, Vice President of Biometrics, to sign on behalf of Michael Edwardes.

Peer Review Biostatistician:

Francis Tang
[redacted]
Everest Clinical Research Corporation

Francis Tang
25 Oct 2024 12:25:09 (-04:00)
REASON: I approve this document.
7ceff508-b0bf-428b-8092-b96c1846754e

Signature **Date**

Approved by:

Yong Tang
[redacted]
Alector Incorporated

Yong Tang
25 Oct 2024 12:43:43 (-04:00)
REASON: I approve this document.
1fbe6cc4-d47b-407e-ab54-d89b6464a7a2

Signature **Date**

Approved by:

Arthur Mayorga
[redacted]
Alector Incorporated

Arthur Mayorga
25 Oct 2024 18:16:48 (-04:00)
REASON: I approve this document.
c0c8c8d4-27fe-4689-8eed-59417ccb7f59

Signature **Date**

TABLE OF CONTENTS

LIST OF TABLES

GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
[^{18}F]MK-6240	fluorine-18 MK-6240
AD	Alzheimer's disease
ADA	antidrug antibodies
ADAS-Cog13	Alzheimer's disease assessment scale-cognitive subscale
ADCOMS	Alzheimer's disease composite score
ADCS-ADL-MCI	Alzheimer's disease cooperative study-activities of daily living – mild cognitive impairment
ADNI	Alzheimer's Disease Neuroimaging Initiative
AE	adverse event
AESI	adverse event of special interest
anti-HBcA	total hepatitis B core antibody
APOE	apolipoprotein E
APOE e4	apolipoprotein E epsilon 4
ARIA	amyloid-related imaging abnormality
ARIA-E	amyloid-related imaging abnormality – edema
ARIA-H	amyloid-related imaging abnormality – hemosiderin deposits
ARS	all randomized set
ATC	anatomic therapeutic class
Aβ, Ab	amyloid beta
Aβ40, Ab40	amyloid beta (1-40)
Aβ42, Ab42	amyloid beta (1-42)
B12	vitamin B12
BLQ	below the limit of quantification
BMI	body mass index
BMW	brain MRI worksheet
BP	blood pressure
CDR	clinical dementia rating
CDR-GS	clinical dementia rating – global score
CDR-SB	clinical dementia rating – sum of boxes
CFB	change from baseline
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
COA	clinical outcome assessment
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization

Abbreviation	Term
CSF	cerebrospinal fluid
CSF1R	colony-stimulating factor-1 receptor
CSR	clinical study report
C-SSRS	Columbia suicide severity rating scale
CV	Coefficient of variation
ECG	electrocardiogram
EFU	efficacy follow-up
eGFR	estimated glomerular filtration rate
EOI	end of infusion
EoS	end of study
ET	early termination
FAS	full analysis set
FLAIR	fluid-attenuated inversion recovery
FSP	fixed sequence procedure
GFAP	glial fibrillary acidic protein
GRE	gradient-recalled echo
HbA1C	hemoglobin A1C
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL	high density lipoprotein
HIV	human immunodeficiency virus
IA	interim analysis
iADRS	modified integrated Alzheimer's disease rating scale
iDMC	independent data monitoring committee
Ig	immunoglobulin
IL1RN	interleukin 1 receptor antagonist
INR	international normalized ratio
IV	intravenous(ly)
LDL	low density lipoprotein
LLOQ	lower limit of quantitation
LP	lumbar puncture
LTE	long-term extension
Max	maximum
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCI	mild cognitive impairment
MCV	mean corpuscular volume
MDRD	modification of diet in renal disease
MedDRA	medical dictionary for regulatory activities

Abbreviation	Term
Min	minimum
mmHg	millimeter of mercury
MMSE	mini-mental status examination
MRI	magnetic resonance imaging
msec	millisecond
MTBR	microtubule-binding region
NfL	neurofilament light chain
NRC	National Research Council
OCT	optical coherence tomography
PCFB	percent change from baseline
PCS	potentially clinically significant
PD	pharmacodynamic
PE	physical examination
PET	positron emission tomography
PK	pharmacokinetic
PPS	per-protocol analysis set
PT	preferred term
pTau	phosphorylated tau
Q1	25th quartile
Q3	75th quartile
q4w	every 4 weeks
QA	quality assurance
QC	quality control
QTcF	QT interval corrected using the Fridericia formula (QTcF = QT/(RR)1/3)
RBANS	repeatable battery for the assessment of neuropsychological status
RDVF	research diagnostic verification form
RNA	ribonucleic acid
ROI	region of interest
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	Statistical Analysis Software, SAS Institute
SD	standard deviation
SEM	standard error of the mean
SFU	safety follow-up
SI	international system
SOC	system organ class
SOP	standard operating procedure
SS	safety set

Abbreviation	Term
SUVR	standardized uptake value ratio
tTau	total tau
TC	Titration Cohort
TEAE	treatment-emergent adverse event
TMEM106b	transmembrane protein 106b
sTREM2	soluble triggering receptor expressed on myeloid cells 2
TPTD	treatment period termination date
ULOQ	upper limit of quantitation
WCCF	worst case carried forward
WGS	whole genome sequencing
WHO DD	World Health Organization Drug Dictionary
WLSA	Winterlight Labs speech assessment
WOCF	worst observation carried forward
WOCBP	woman of childbearing potential
YKL-40	chitinase-3-like protein 1

1. INTRODUCTION

This statistical analysis plan (SAP), for analysis to be performed at the time of unblinding of the AL002-2 (Core) Study, other interim analyses, and final analysis, outlines the statistical methods for the display, summary and analysis of data collected within the scope of Alector Inc. Protocol AL002-LTE, Version 2.0, dated 20 January 2024; and, for integrated analyses, the additional source is Protocol AL002-2, Version 7.0, dated 20 June 2023. AL002-2 is referred to as the Core Study and AL002-LTE is referred to as the long-term extension (LTE) Study throughout the SAP.

Deviations from this SAP must be substantiated by a sound statistical rationale and will be documented in the clinical study reports (CSRs). If there are differences between the protocols and the SAP, this SAP will take precedence.

The SAP should be read in conjunction with the study protocols and the case report forms (CRFs). This version of the SAP has been developed using version 2.0 of the annotated CRFs for AL002-LTE dated 09 May 2024, and version 10.0 of the annotated CRFs for AL002-2 dated 21 March 2024.

The purpose of this SAP is to provide general guidelines from which the analyses will proceed for both the LTE Analysis and the Integrated Analysis. The LTE Analysis specified in this SAP refers to the summary or analysis of the data collected in the LTE Study and baseline data from the Core Study depending on the treatment group and/or summary/analysis. The Integrated Analysis specified in this SAP refers to the summary or analysis over the integrated data collected from the Core Study and the LTE Study.

Analysis Visit weeks referred to in the SAP are labelled differently than the “nominal” names given in the protocols, at one week less. Thus, nominal Week 25 in the protocol is Analysis Week 24 in the SAP, and nominal Week 49 in the protocol is Analysis Week 48 in the SAP (refer to Section 7.1.1.2 for analysis visit definitions).

2. STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are provided in Table 2-1.

Table 2-1. Study Objectives, Endpoints and Estimands for LTE

Primary Objectives	Primary Safety Endpoints and Primary Estimand

To evaluate the long-term safety and tolerability of AL002 in participants with AD.	*Part 1: Primary Safety Endpoint and Estimand:*
	• Treatment condition: Group T-T (AL002 15 mg/kg, 40 mg/kg or 60 mg/kg IV Q4W) continues their Core Study treatment in the LTE Study; Group P-TC treated with Placebo in the Core study will be titrated to 60 mg/kg of AL002 in the LTE study.
	• Target population: adult participants with AD excluding apolipoprotein E (APOE) epsilon 4 (e4)-homozygous (e4/e4) participants.
	• Primary endpoints: AESI incidence and SAE incidence over all weeks.
	• Accounting for intercurrent events: a composite strategy will be used to handle intercurrent events as below:
	  ○ Hypothetical strategy for handling premature study drug discontinuation for any reason (AEs with a start date more than 90 days after study drug discontinuation are not counted)
	  ○ Treatment policy strategy for handling all other intercurrent events.
	• Population-level summaries: the descriptive statistical summaries for each treatment group of incidence rates for all AESIs and SAEs over similar periods of time.
	Part 2: Primary Safety Endpoints:
	• Changes from baseline (CFBs) in vital signs, physical findings, neurological findings, ophthalmological findings, ECG findings, and clinical laboratory results.
	• MRI abnormalities (ARIA events)
	• C-SSRS.
	Primary Estimand for Safety Endpoints Above:
	The estimand for the Part 2 endpoints is defined with similar attributes as for the Part 1 estimand except applied to the different endpoints

DocUUID : 7f778de0-046e-479d-bb51-d30ce4769ceb

Primary Objectives	Primary Safety Endpoints and Primary Estimand
To evaluate the effect of dose titration on ARIA in participants with AD	*Part 3: Primary Endpoints*: • Incidence and severity of ARIA in participants undergoing titration *Primary Estimand for Incidence and Severity of ARIA:* The estimand for incidence and severity is defined with similar attributes as for the Part 1 primary estimand except that it is applied to incidence and severity of ARIA, and difference in incidence of ARIA events between slower and faster titration groups will be reported
Secondary Objective	**Secondary Endpoints**
To evaluate the PK of AL002 in participants with early AD	• Serum PK concentrations of AL002 and relevant PK parameters.
To evaluate the effects of AL002 with COAs in participants with AD	*LTE Efficacy Endpoints:* • Disease progression as measured by the CFB in CDR-SB score. • CFB in MMSE score. • CFB in RBANS score. • CFB in ADAS-Cog13 score. • CFB in ADCS-ADL-MCI score. • CFB in ADCOMS. • CFB in modified iADRS. *Main Estimand for Efficacy:* The main estimand for the LTE Efficacy endpoints is defined with similar attributes as for the primary safety estimand in Part 1 except the following. • Accounting for intercurrent events: a composite strategy will be used to handle intercurrent events as below: o Hypothetical strategy for handling premature study drug discontinuation for any reason (data will be considered missing after early discontinuation of study drug plus 37 days). o Treatment policy strategy for handling all other intercurrent events. • Population-level summary: the percent reduction relative to placebo decline (the proportional treatment effect), comparing each dose level to placebo.

Primary Objectives	Primary Safety Endpoints and Primary Estimand
Exploratory Objectives	**Exploratory Endpoints**
To evaluate the effects of AL002 on biomarkers in participants with AD	*Biomarker Endpoints* • CFBs in levels of sTREM2 in CSF and/or plasma. • CFBs in levels of biomarkers related to microglia function in CSF and/or plasma including but not limited to CSF1R, IL1RN, osteopontin, and YKL-40. • CFBs in levels of biomarkers related to AD pathology in CSF and/or plasma including but not limited to Aβ40, Aβ42, pTau, and tTau. • CFBs in levels of neurodegeneration biomarkers in plasma and CSF including but not limited to NfL. • CFBs in brain volume, assessed by volumetric MRI. • CFBs in brain pathological tau burden as assessed by Tau-specific PET, only for participants who agree to participate in the optional assessment. • CFBs in brain amyloid burden as assessed by longitudinal Amyloid PET scanning, only for participants who agree to participate in the optional assessment. For the exploratory biomarker endpoints, the *Main Estimand* for exploratory efficacy endpoints applies for LTE analyses, which has the same definition as the Main Estimand for Efficacy. For integrated analyses, however, differences between Placebo and AL002-treated groups are analyzed for Core study data adding the LTE screening data for placebo and the LTE data for Group T-T, and the applicable estimand is the main estimand applied to estimated CFB differences between placebo and treated groups.
To evaluate the effect of immunogenicity to AL002 in participants with AD	• Incidence of ADAs. For this endpoint, the estimand for safety endpoints applies.

Aβ40=amyloid beta (1-40); Aβ42=amyloid beta (1-42); AD=Alzheimer's disease; ADA=anti-drug antibodies; ADAS-Cog13=Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS=Alzheimer's Disease Composite Score; ADCS-ADL-MCI=Alzheimer's Disease Cooperative Study – Activities of Daily Living – Mild Cognitive Impairment Scale; AE=adverse event; AESI=adverse event of special interest; CDR-SB=Clinical Dementia Rating – Sum of Boxes; COA=clinical outcome assessment; CFB=change from baseline; CSF=cerebrospinal fluid; CSF1R=colony stimulating factor 1 receptor; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; iADRS=integrated Alzheimer's Disease Rating Scale; IL1RN=interleukin 1 receptor antagonist; MMSE=Mini-Mental Status Examination; MRI=magnetic resonance imaging; NfL=neurofilament light; PET=positron emission tomography; PK=pharmacokinetic(s); pTau=phosphorylated tau; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status-Update; SAE=serious adverse event; sTREM2=soluble triggering receptor expressed on myeloid cells 2; tTau=total tau; YKL-40=chitinase 3-like protein 1.

3. STUDY DESIGN

3.1 Study Design

This is a Phase 2, LTE study of participants with AD. The study will enroll participants who completed the planned treatment period in AL002-2 (Core Study). Study sites are located in North America, Australia, Europe, and Argentina.

Participants who were randomized to active treatment in the Core Study will remain on their previously assigned dose. Participants who were previously on placebo in the Core Study will be assigned to the Titration Cohort (TC), which will initiate with a starting dose of either 2 mg/kg or 6 mg/kg that will be increased over 32 weeks or 24 weeks, respectively, to reach the target dose of 60 mg/kg per the Titration Algorithm (for details of the Titration Algorithm, refer to the Study Protocol).

The planned duration of the LTE study is 56 weeks, and LTE study treatment extends from LTE Day 1 to Week 48. Dosing duration may be extended beyond this time through a protocol amendment, within the context of emerging favorable safety data. AL002 will be administered via IV infusion at the study site on Day 1 (after all necessary baseline assessments have been completed) and will be repeated subsequently once every 4 weeks throughout the treatment period.

The first dose of the AL002-LTE should be within the 4-week window (±5 days) of the last dose of the Core Study, to maintain continuity of study treatment. Delays of the first AL002-LTE dose beyond that window will constitute protocol deviations.

Dosing for any individual participant may be stopped, paused, or reduced based on emerging safety data and/or the development of ARIA-E or ARIA-H. If a participant discontinues the study prior to the end of their planned treatment period, they will need to return for an Early Termination (ET) Visit and that will mark the end of their participation in the study.

At study entry and throughout the treatment period, safety will be assessed through monitoring of AEs (including AESIs and SAEs), changes in laboratory and vital sign values, incidence of findings from physical, neurological, ECG, MRI, ophthalmological exams, and reports of suicidal ideation or behavior. Serum PK will be assessed for investigation of exposure-response and exposure-safety relationships. Blood samples for assessment of ADA will be taken throughout the study.

The COAs, PK assessments, and biomarker assessments (fluid collection and imaging) will be performed prior to dosing and at specific time points during the treatment period and at End of Study (EoS)/ET if needed.

3.2 Participant Grouping

There are two treatment classes for the LTE and Integrated Analyses:

- **Group T-T** includes participants who were exposed to AL002 during the Core Study. They will continue at their Core Study AL002 dosage during the LTE Study if enrolled in the LTE Study. Group T-T is further broken down as AL002 15 mg/kg, 40 mg/kg, and 60 mg/kg treatment groups.

- **Group P-TC** includes participants who were exposed only to placebo during the Core Study. They will be assigned to the TC during the LTE Study if enrolled in the LTE Study. Group P-TC might be separated into placebo and TC treatment groups depending on the summaries/analyses.

  For Group P-TC, the data collected when the participants were receiving placebo in the Core Study might be summarized and/or analyzed separately from the data collected once the participants received the first study drug administration in the LTE Study. The data collected when the participants were receiving placebo in the Core Study up to the day before the participants received the first study drug administration in the LTE Study (separately from the data collected in the LTE Study) is referred to as **the Placebo Data** throughout the SAP. And it includes the data from the placebo participants who did not enroll in the LTE Study. The data collected on or after the day when the participants received the first study drug administration in the LTE Study is referred to as **the TC Data** throughout the SAP.

The first dose date of AL002 refers to the earliest date of any amount of AL002 administered across the Core Study and the LTE Study. **The last dose date of AL002** refers to the latest date of any amount of AL002 administered across the Core Study and the LTE Study. **The first dose date of any study drug** refers to the earliest date of any study drug administered, including placebo, across the Core Study and the LTE Study.

3.3 Randomization

Not applicable. Participants are categorized per their assigned treatment groups in the Core Study.

3.4 Hypothesis Testing

There are two hypotheses to be tested. First there is the efficacy null hypothesis of the core study:
The null and alternate hypotheses for comparing each of the treatment groups to placebo are as follows:

H_0 (null): $\theta \leq 0$, indicating that treatment does not slow disease progression relative to placebo control,
H_1 (alternative): $\theta > 0$, indicating that treatment slows disease progression relative to placebo control,

where θ represents the treatment effect, defined as a proportional reduction of the placebo group clinical decline in the CDR-SB.

Secondly, there is a test of the null hypothesis that dose titration speed has no effect on occurrence of first ARIA events. The null and alternate hypotheses for comparing treatment with slower titration against treatment with faster titration are:

H_0 (null): $\tau = 0$, indicating that slower titration does not change first ARIA event incidence relative to treatment with faster titration,
H_1 (alternative): $\tau \neq 0$, indicating that slower titration changes first ARIA event incidence relative to treatment with faster titration,

where τ represents the slower titration effect, defined as difference in first ARIA event incidence relative to the group with faster titration.

3.5 Sample Size

It is expected that 80% to 90% of the participants who completed the planned treatment period in the Core Study and are not APOE e4/e4 will enroll in the LTE Study. Currently, there are 220 such participants in the Core Study who either completed planned treatment or are ongoing, so 176 to 198 participants are expected.

4. DATA AND ANALYTICAL QUALITY ASSURANCE

The overall quality assurance procedures for the study data, statistical programming and analyses are described in Everest's Standard Operating Procedures. Detailed statistical and programming quality control (QC) and quality assurance (QA) procedures are documented in the Statistical Analysis and Programming QC/QA Plan.

The study endpoints and analytic approaches are both prospectively defined and documented in the protocol and in this SAP. The SAP will be finalized prior to the Core Study database lock.

DocUUID : 7f778de0-046e-479d-bb51-d30ce4769ceb

5. ANALYSIS SETS

When change (or percent change) from baseline is assessed, participants will be included in applicable analysis sets and in the analysis only if the participants had both a baseline and a postbaseline measure.

5.1 As-Treated Set (ATS)

The ATS is the same as the ATS of the Core Study and consists of all participants who received any amount of study drug administration in the Core Study.

All analyses using the ATS will group participants according to the highest dose level of AL002 received as determined in the Core Study (i.e., AL002 15 mg/kg, 40 mg/kg, or 60 mg/kg), except for Group P-TC. Participants in Group P-TC will remain in Group P-TC regardless of the highest dose level received, but they will be presented as two groups: Placebo (for data during placebo treatment) and Titration Cohort (for data during LTE titration). This grouping is referred to as actual treatment.

5.2 Analysis Sets Excluding APOE e4-homozygous (e4/e4) Participants

5.2.1 Non-e4/e4 Set

The Non-e4/e4 Set is the same as the Non-e4/e4 Set of the Core Study and consists of all participants who received any amount of study drug administration in the Core Study and who are not APOE e4/e4 (i.e., non-e4/e4).

All analyses using the Non-e4/e4 Set will group participants as described above for the ATS.

5.2.2 As-Treated Set – LTE (ATS-LTE)

The ATS-LTE consists of all participants who received any amount of study drug administration in the LTE Study. No e4/e4 participants were enrolled in the LTE Study.

All analyses using the ATS-LTE will group participants as described above for the ATS.

5.2.3 Full Analysis Set (FAS)

The FAS is the same as the FAS of the Core Study and consists of all participants who were randomly assigned in the Core Study, received any amount of study drug, and are non-e4/e4.

A participant's status of APOE e4 and APOE genotype will be determined by the APOE genotype central laboratory data provided by the vendor in the Core Study. If a participant's APOE genotype is not e4/e4, then the participant is not APOE e4-homozygous (i.e., the participant is a non-e4/e4 participant). In other words, the FAS excludes e4/e4 participants.

All analyses using the FAS will group participants either to the assigned treatment in the Core Study (i.e., AL002 15 mg/kg, 40 mg/kg, or 60 mg/kg) or to Group P-TC, but they will be presented as two groups: Placebo/TC (for analyses using Core Study Baseline) and Titration Cohort (for data during LTE titration using LTE Study Baseline).

5.2.4 Pharmacokinetic Set (PKS)

The Pharmacokinetic Set will include all participants in the ATS that received AL002, had at least one post-dose measurable concentration, and are non-e4/e4.

All analyses using the PKS will group participants as described above for the ATS.

6. SPECIFICATION OF ENDPOINTS AND VARIABLES

6.1 Demographics and Baseline Characteristics

The Core baseline is the baseline defined and used in the Core Study (refer to the AL002-2 SAP for details).

Selection of the LTE baseline is specified in Section 7.1.2.

The **last participation date** is the date of last visit (any scheduled, unscheduled, EOS, ET, EFU, or SFU visit) or AE assessment during the study.

6.1.1 Demographics and Baseline Characteristics

Demographic information, including year of birth, age at time of informed consent (in years), sex, race, ethnicity and handedness are collected at the Screening visit of the Core Study and might be updated during the Screening period of the LTE Study.

Weight and height are collected at the Screening visit for the Core Study and might be updated during the Screening period of the LTE Study, if not collected at the final visit of the Core Study. Weight will be collected throughout the LTE Study. Body mass index (BMI) will be calculated as the weight in kg divided by the square of height in meters.

Age at AD diagnosis will be calculated from the date of diagnosis and birth year as {(year of diagnosis) – (year of birth)} as collected at the Screening visit of the Core Study and will not be updated for the LTE Study.

Time since AD diagnosis will be calculated from the date of diagnosis and informed consent date as {(informed consent date) – (AD diagnosis date) / 365.25} and will be updated for the Titration Cohort as being based on LTE informed consent date. If AD diagnosis date is partially missing, unknown day will be imputed as the 1st, and unknown month will be imputed as January.

The countries where a participant is enrolled in the Core Study at will be grouped into geographical region, namely, United States and rest of the world.

A participant's APOE e4 status and APOE genotype will be determined by the APOE genotype central laboratory data provided by the vendor in the Core Study. If a participant's APOE genotype contains "e4", the participant is considered an e4 carrier (or carrier); otherwise, a non-carrier.

The PD biomarker assessments will consist of blood-based biomarkers, CSF-based biomarkers (optional sub-study), and imaging biomarkers (MRI efficacy, sub-studies of amyloid PET, and Tau PET) and will

be collected during screening or pre-dose of the Core Study and the LTE Study. Other timing and frequency of all PD biomarker assessments are presented in the Schedules of Assessments in protocols.

Demographic variables will include the following:

- Age (years) at time of informed consent in the LTE Study as a continuous variable and as categories
  - Age group 1
    - < 65 years
    - ≥ 65 years
    - Missing (including blank, not reported, unknown, etc.)
  - Age group 2
    - < 65 years
    - ≥ 65 – < 75 years
    - ≥ 75 years
    - Missing (including blank, not reported, unknown, etc.)
- Sex
  - Female
  - Male
  - Missing (including blank, not reported, unknown, etc.)
- Race
  - American Indian or Alaska Native
  - Asian
  - Black or African American
  - Native Hawaiian or Other Pacific Islander
  - White
  - Multiple
  - Missing (including blank, not reported, unknown, etc.)
- Ethnicity
  - Hispanic or Latino
  - Not Hispanic or Latino
  - Missing (including blank, not reported, unknown, etc.)
- Handedness
  - Always Right
  - Usually Right
  - Either Hand
  - Usually Left
  - Always Left
  - Missing (including blank, not reported, unknown, etc.)
- Weight (kg)
- Height (cm)
- BMI (kg/m2) as a continuous variable and as categories
  - < 18.5 kg/m^2
  - 18.5 – < 25.0 kg/m^2
  - 25.0 – < 30.0 kg/m^2
  - ≥ 30.0 kg/m^2

- Geographical region
  - United States
  - Rest of World

Baseline disease characteristics and baseline COAs will include the following:

- Age at AD diagnosis (years)
- Time since AD diagnosis (years)
- APOE e4 status
  - Carrier
  - Non-carrier
  - Missing (including blank, not reported, unknown, etc.)
- APOE genotype
  - e2/e3
  - e2/e4
  - e3/e3
  - e3/e4
  - Missing (including blank, not reported, unknown, etc.)
- AD diagnosis
  - Mild Cognitive Impairment (MCI) due to Alzheimer's disease
  - Mild Dementia due to Alzheimer's disease
- Baseline clinical dementia rating – global score (CDR-GS) as a continuous variable and as categories
  - 0.5
  - 1
  - Missing (including blank, not reported, unknown, etc.)
- Baseline CDR-SB
- Baseline MMSE
- Baseline RBANS
- Baseline ADAS-Cog13
- Baseline ADCS-ADL-MCI score
- Baseline ADCOMS
- Baseline modified iADRS

6.1.2 Prior and Concomitant Medications/Treatments

6.1.2.1 Prior and Concomitant Medications/Treatments for Placebo Data

For the Placebo data as specified in Section 3.2, the prior and concomitant medications are defined the same way as in the Core Study SAP.

6.1.2.2 Prior and Concomitant Medications/Treatments for AL002 Dosed Participants

For participants who are ever exposed to AL002, a medication will be considered as "*prior*" if the end date of administration is before the first dose date of AL002 as specified in Section 3.2.

Any medication with a start date prior to or on the first dose date of AL002 and continued after the first dose date of AL002 or started after the first dose date of AL002 but prior to or on the last dose date of AL002 as specified in Section 3.2 will be considered concomitant medications. Medications started and stopped on the same day as the first dose date or the last dose date of AL002 will also be considered concomitant. Medications with an end date prior to the date of first dose date of AL002 or a start date after the last dose date of AL002 will be excluded from the concomitant medication summary. If a partial end date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the first dose date of AL002 will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the last dose date of AL002 will be excluded from the concomitant medication summary. Medications with completely missing start and end dates will be included in the concomitant medication summary, unless otherwise specified.

The World Health Organization Drug Dictionary (WHO DD), version March 2020 or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name.

6.1.2.3 Uncoded Medication

All medications are expected to be coded by the anatomic therapeutic class (ATC) for the interim and final analyses. Any uncoded records as of the data cutoff for analysis will be assigned the string "UNCODED" as the anatomic therapeutic class (ATC) code, and the verbatim term will be used as the preferred term (PT), so they can be included in the summary tables.

6.1.2.4 Multiple ATC Assignments

If there are multiple ATC codes assigned to the same concomitant medication, the "primary" one based on a Sponsor authorized medical code will be used.

6.2 Safety Endpoints and Variables

Safety variables include the following:

- AEs, AESIs, and SAEs
- C-SSRS
- CFBs in hematology and chemistry
- CFBs in urinalysis
- CFBs in coagulation
- CFBs in ECG
- CFBs in vital signs
- MRI abnormalities

- CFBs in neurological examination
- CFBs in ophthalmological examination
- CFBs in physical exam

6.2.1 Extent of Exposure to Study Drug and Treatment Compliance

In the LTE Study, all participants will receive intravenous (IV) administration of AL002 on LTE Study Day 1 and then q4w (every 4 weeks) for a minimum 13 doses over a 48-week period, according to the Schedules of Assessments in the LTE protocol.

For Integrated Analysis, definitions are as follows. For LTE Analysis, these definitions are restricted to exposure, doses and compliance at and after first AL002 dose in the LTE Study.

Duration of Exposure

Duration of exposure (day) is defined as the total number of days that a participant is exposed to any amount of study drug (AL002 or placebo), regardless of any temporary interruptions in study drug administration,

For integrated analysis, duration of exposure (days) = min (last dose date + 28, death date + 1) - first dose date in the core study, where the first and last dose date of study drug are defined in Section 3.2. 28 days (q4w) is the study drug administration (IV) interval.

The first and last dose dates of placebo are the same as those dates in the Core study.

Duration of exposure (week) is defined as the duration of exposure to study drug in days divided by 7.

Duration of exposure (month) is defined as the duration of exposure to study drug in days divided by 30.4375.

Duration of exposure (years) is defined as the duration of exposure to study drug in days divided by 365.25.

Duration of Exposure to AL002

Duration of exposure to AL002 is defined as above for duration of exposure to study drug, but placebo is excluded from the definition.

Duration of LTE Exposure to AL002

Duration of exposure to AL002 (day) in the LTE Study will be calculated as

Duration of exposure (days) = min (last dose date + 28, death date + 1) - first dose date in the LTE study.

Total Number of Doses Received

The total number of study drug doses received is defined as the total number of doses of any amount of study drug that a participant received as recorded on the Exposure – IV electronic CRF.

Treatment Compliance

Treatment compliance is defined as the total cumulative received IV volume of study drug (mL) divided by the total cumulative expected IV volume (mL), and then multiplied by 100. The total cumulative expected IV volume will be the sum of the expected IV volume while they are on study treatment across all planned study days, up to the date of withdrawal, if participant discontinued study drug early. For compliance during the LTE Study, compliance is restricted to LTE visits.

The formula for calculation is as follows:

$$\text{Treatment Compliance} = 100 \times \frac{total\ cumulative\ received\ IV\ volume\ (mL)}{total\ cumulative\ expected\ IV\ volume\ (mL)}$$

6.2.2 Adverse Events

All AEs will be collected after the participant signs the informed consent form. AEs will be characterized by seriousness, special interest, severity, relationship to study drug, and outcome.

AEs will be collected and coded by system organ class (SOC) and PT using MedDRA, Version 23 or newer.

6.2.2.1 Treatment-Emergent Adverse Events

6.2.2.1.1 *Treatment-Emergent Adverse Events for Placebo Data*

For the Placebo Data as specified in Section 3.2, the treatment-emergent AEs (TEAEs) are defined the same way as in the Core Study SAP. And handling of incomplete dates is specified in the Core Study SAP.

6.2.2.1.2 *Treatment-Emergent Adverse Events for AL002 Dosed Participants*

For participants who were ever exposed to AL002, AEs that occur on or after the first dose date of AL002 and up to 90 days after study drug discontinuation will be considered TEAEs.

- If both the start time of the AE and the time of the first AL002 administration are available, an AE is considered a treatment-emergent AE (TEAE) if its start date and time are on or after the first AL002 administration and no later than 90 days after the last dose date of AL002. The last dose date of AL002 is defined in Section 3.2.

- If either the start time of the AE or the time of the first AL002 administration is unavailable, an AE is considered a TEAE if its start date is on or after the first dose date of AL002 and no later than 90 days after the last dose date of AL002. Handling of incomplete dates is specified in Section 6.2.2.6.

6.2.2.2 Adverse Events of Special Interest

An AE of special interest (AESI) is a serious or nonserious AE that is of scientific and medical concern specific to a product for which ongoing monitoring and rapid reporting by the Investigator to the Sponsor should occur. AESI for this study are defined as the following occurrences:

- Amyloid-related imaging abnormality – hemosiderin deposits (ARIA-H)
- Amyloid-related imaging abnormality – edema (ARIA-E)

- Uveitis

6.2.2.3 Serious Adverse Events

SAEs will be identified and captured as SAEs for AEs that meet the definition of SAE that is specified in the protocol.

6.2.2.4 Relationship of Adverse Events to Study Drug

Related AEs are those for which the Investigator selected "Related" on the AE electronic CRF to the question whether an event is related to study drug. Relatedness will always default to the Investigator's choice, not that of the medical monitor.

6.2.2.5 Relationship of Adverse Events to Radiotracers

TEAEs that are related to radiotracers will not be summarized or listed for this LTE Analysis.

6.2.2.6 Handling of Incomplete Dates for AL002 Dosed Participants

If the start date of the AE is incomplete and the AE end date is not prior to the first dose date of AL002, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE start date is the same as or after the month and year (or year) of the first dose date of AL002, and
- The AE start date is the same as or before the month and year (or year) of the date corresponding to 90 days after the last dose date of AL002.

An AE with completely missing start and end dates, or with the start date missing and an end date later than the first dose date of AL002, will be considered treatment emergent. In addition, an AE with the start date missing and incomplete end date with the same or later month and year (or year alone if month is not recorded) as the first dose date of AL002 will be considered treatment emergent.

An imputation will be done for partial dates in order to compute an estimated study day for display in the listing. For partial start dates:

- If the year is unknown, then the date will be assigned the first dose date of AL002.
- If the month is unknown, then:
  a) If the year matches the year of the first dose date of AL002, then the month and day of the first dose date will be imputed.
  b) Otherwise, 'January' will be assigned.
- If the day is unknown, then:
  a) If the month and year match the month and year of the first dose date of AL002, then the day of the first dose date will be imputed.
  b) Otherwise, '01' will be assigned.

For partial end dates:

- If the year is unknown, then the date will be assigned the last participation date of AL002.
- If the month is unknown, then:
  a) If the year matches the year of the last participation date of AL002, then the month and day of the last participation date will be imputed.
  b) Otherwise, "December" will be assigned.
- If the day is unknown, then:
  a) If the month and year match the month and year of the last participation date of AL002, then the day of the last participation date will be imputed.
  b) Otherwise, the last day of the month will be assigned.

If the imputation takes the start date past the known end date, then the start date will be set to the day before the end date. If the imputation takes the end date prior to the known start date, then the end date will be set to the day after the start date.

The first dose date of AL002 is defined in Section 3.2.

6.2.2.7 Deaths

Deaths will be captured as SAEs according to the methods described above.

6.2.3 Columbia-Suicide Severity Rating Scale (C-SSRS)

Two versions of the C-SSRS were used in the Core Study: a Screening/Baseline version and a Since Last Visit version. The Screening/Baseline version of the C-SSRS assesses the lifetime suicidal ideation and behavior and non-suicidal self-injurious behavior, the suicidal ideation in the past 6 months and suicidal behavior and non-suicidal self-injurious behavior in the past 2 years. The Screening/Baseline version of the C-SSRS was administered on Core Study Day 1 prior to dosing. The Since Last Visit version of the C-SSRS assesses suicidal thoughts or behaviors the participant may have had since the last time the C-SSRS was administered as specified in the Schedules of Assessments in the protocol.

6.2.4 Laboratory Data

Collection schedules for hematology, blood chemistry, urinalysis testing, and coagulation are specified in the Schedules of Assessments in the protocols.

Indicators of values below or above a limit of quantitation (the lower limit of quantitation (LLOQ) or the upper limit of quantitation (ULOQ)) will be included, as well as all LLOQ or ULOQ limits. When values are below or above a limit of quantitation, they will be listed as such, and the closest imputed value will be used for calculating summary statistics as specified in Section 7.1.4.

Laboratory results will be assigned toxicity grades by the central laboratory based on the Common Toxicity Criteria for AEs (CTCAE) V5.0, when applicable. For a laboratory test, if the alert flag was normal and the toxicity grade was absent, then the toxicity grade will be assigned zero, and it is not considered as missing or unknown.

The tests performed are shown below in

Table 6-1 Clinical Laboratory Safety Assessments

.

6.2.4.1 Conversion to the International System of Units

All laboratory data will be stored in the database with the units in which they are originally reported. Laboratory data in summary tables and by-participant data listings will be presented in the International System of Units (SI units; Système International d'Unités). Laboratory data not reported in SI units will be converted to SI units before further processing or data analysis, unless otherwise specified.

Table 6-1 Clinical Laboratory Safety Assessments

Test	Analytes
Hematology	Absolute neutrophil count, hemoglobin, hematocrit, MCH, MCV, MCHC, white blood cells, red blood cells, platelet count, and differential count (neutrophils, lymphocytes, monocytes, basophils, eosinophils).
Chemistry (serum or plasma)	Sodium, potassium, chloride, calcium, glucose, bicarbonate, albumin, total protein, creatinine, HbA1C, blood urea nitrogen or urea, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase, phosphorous, total bilirubin (direct and indirect), amylase, cholesterol (total, LDL, HDL), triglycerides, uric acid, creatine phosphokinase, lactate dehydrogenase, magnesium, C-reactive protein. Thyroid-stimulating hormone, folic acid, vitamin B12, and viral serology (HIV-1 or HIV-2 antibody and antigen, hepatitis B surface antigen, total hepatitis B core antibody, HCV antibody/RNA) will also be assessed at screening only.
Coagulation	Prothrombin time with INR, activated partial thromboplastin time
Urinalysis	Dipstick (pH, specific gravity, glucose, protein, ketones, blood). Microscopic analysis in the event of abnormal dipstick results (urinary sediment, red blood cells, white blood cells, casts, crystals, epithelial cells, bacteria).

Abbreviations: HbA1C =hemoglobin A1C; HCV=hepatitis C virus; HDL=high density lipoprotein; HIV=human immunodeficiency virus; INR=international normalized ratio; LDL=low density lipoprotein; MCH=Mean Corpuscular Hemoglobin; MCHC=Mean Corpuscular Hemoglobin Concentration; MCV=Mean Corpuscular Volume.

6.2.5 Electrocardiogram (ECG)

Single 12-lead ECGs including heart rate, QRS (Q wave, R wave, S wave) duration, QT interval (beginning of Q wave to end of T wave) corrected using the Fridericia formula (QTcF interval), RR interval (time between 2 successive R waves) and result interpretation will be captured on the electronic CRF. The investigator will assess and document whether the ECG is "Normal", "Abnormal not clinically significant", "Abnormal clinically significant" or "Not evaluable".

ECG parameters will include the following:

- Heart Rate (beats/min)
- QRS duration (msec)

- RR Interval (msec)
- QTcF Interval (msec)
- Interpretation

6.2.6 Vital Signs

Vital signs (supine systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and temperature) will be measured at all visits. Height will be collected at Screening of both studies. Weight will be collected at scheduled visits (refer to the protocols for scheduled visits).

Vital signs parameters will include the following:

- Weight (kg)
- Systolic Blood Pressure (millimeter of mercury (mmHg))
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (beats/min)
- Respiratory Rate (breaths/min)
- Temperature (C)

6.2.7 Magnetic Resonance Imaging (MRI) for Detection of ARIA-E and ARIA-H

A brain MRI will be performed to detect brain abnormalities, such as ARIA-E and ARIA-H.

For Integrated Analysis, definitions follow the definitions in the Core Study SAP. For LTE Analysis, definitions follow below. Note that these are restricted to events at or after the first AL002 dose in the LTE Study.

6.2.7.1 ARIA-E

6.2.7.1.1 *Event Definition*

An event of ARIA-E is defined as an MRI scan where the Brain MRI Worksheet (BMW) shows the presence of vasogenic edema.

6.2.7.1.2 *Severity Definition*

ARIA-E severity is based on radiographic severity as captured on BMWs.

6.2.7.1.3 *Resolution and Time to Resolution Definition*

- ARIA-E is considered resolved for a participant if all the subsequent MRI scans showed no ARIA-E following the last MRI scan showing ARIA-E.
- Time to resolution is defined as the number of days from the exam date of the first MRI scan showing ARIA-E to the exam date of the earliest MRI showing no ARIA-E after the last one showing ARIA-E. If a participant had a resolved but recurrent ARIA-E after the previous one was resolved, both times to resolution are included.
- If there is existing ARIA-E at LTE Baseline, it is not included as a new occurrence during LTE.

6.2.7.1.4 *Time to First Occurrence and Recurrence Definition*

- Time to the first occurrence is defined as the number of days from the first dose date in the LTE Study to the exam date of the first new MRI scan showing ARIA-E.
- For a participant, if there was an MRI scan showing ARIA-E, followed by a subsequent MRI scan not showing ARIA-E, followed by a subsequent MRI scan again showing ARIA-E, this participant is considered to have a reoccurrence of ARIA-E.

6.2.7.2 ARIA-H

For the MRI scans collected in the Core Study, the definitions are specified in the Core Study SAP. Definitions below are for the MRI scans collected in the LTE Study.

6.2.7.2.1 *Event Definition*

For the MRI scans collected in the LTE Study, an event of new ARIA-H is defined as an MRI scan at a post-LTE Baseline visit if the overall ARIA-H radiographic severity is Mild, Moderate or Severe as captured on BMWs.

6.2.7.2.2 *Severity Definition*

For the MRI scans collected in the LTE Study, new ARIA-H overall severity and individual component severity are based on the radiographic severity as captured on BMWs.

6.2.7.2.3 *Time to First Occurrence Definition*

Definition is the same as the time to first occurrence definition for ARIA-E.

6.2.8 Neurological Examination

A complete neurologic examination including the evaluation of consciousness, orientation, cranial nerves, motor and sensory system, coordination and gait, and reflexes will be performed at scheduled visits (refer to the Schedules of Assessments in the protocols for scheduled visits). CFBs abnormalities should be recorded at each subsequent neurologic examination. New or worsened abnormalities should be recorded as AE on the AE electronic CRF if considered clinically significant in the Investigator's opinion.

6.2.9 Ophthalmological Examination

Ophthalmologic exams include the following:

- A visual acuity exam (e.g., using a Snellen chart)
- Slit-lamp examination before and after dilation
- Dilated exam of the fundus by indirect ophthalmoscopy
- Optical coherence tomography (OCT) exam, including enhanced depth imaging OCT for examination of the choroid

Ophthalmological assessments will be recorded at scheduled visits (refer to the Schedules of Assessments in the protocols for scheduled visits). CFBs abnormalities are recorded at each subsequent ophthalmological examination. New or worsened abnormalities should be recorded as AE.

6.2.10 Physical Examination (PE)

Complete PE includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, and gastrointestinal systems. Breast, rectal, and genitourinary exams are performed as clinically indicated.

Limited PE includes cardiovascular, respiratory, and gastrointestinal systems; further symptom-directed examination may also include any other pertinent system as required.

Abnormalities observed at baseline, as well as new or worsened clinically significant abnormalities at all other visits, will be recorded on the electronic CRF. New abnormal PE findings will be followed up at the next scheduled visit. New or worsened abnormalities should be recorded as AE on the AE electronic CRF if considered clinically significant in the Investigator's opinion.

6.2.11 Other Safety Assessments

6.2.11.1 Pregnancy Test

Serum pregnancy tests will be performed for all females of childbearing potential at scheduled visits (refer to the Schedules of Assessments in the protocols for scheduled visits).

6.3 Pharmacokinetic (PK) Endpoints

- Serum PK concentrations of AL002
- CSF PK concentrations of AL002 (when available)

6.4 Efficacy Endpoints and Estimands

6.4.1 Clinical Dementia Rating – Sum of Boxes (CDR-SB)

The Clinical Dementia Rating (CDR) is a global clinical scale with established diagnostic and severity-ranking utility widely used in clinical trials; one component of this scale is the CDR Sum of Boxes (CDR-SB). The CDR-SB is used in AD trials as a global measure of disease severity. The CDR-SB is rated based on participant and informant input. The CDR-SB assesses three domains of cognition (memory, orientation, judgment/problem solving) and three domains of function (community affairs, home/hobbies, personal care) using semi-structured interviews of both the study participant and a companion/informant carried out by a trained rater and scored using a standard methodology. Each domain is rated on a 5-point scale of functioning as follows: (0) no impairment; (0.5) questionable impairment; (1) mild impairment; (2) moderate impairment; (3) severe impairment (personal care is scored on a 4-point scale without a 0.5 rating available). Higher scores indicate greater impairment.

The CDR-SB score is a quantitative general index that provides more precision than the CDR-GS in participants with mild dementia. The CDR-SB score is obtained by summing all of the domain scores and the CDR-SB score ranges from 0 to 18.

If only one box (of 6) of the CDR-SB is missing, the sum of the boxes will be imputed by prorating the sum from the other 5 boxes as follows: the total from the remaining boxes will be multiplied by a factor that includes the maximum score for the missing boxes. For example, if the first box, "Memory" which ranges from a score of 0 through 3 (maximum = 3), is missing, then the multiplication factor = 18/(18 - 3)

= 18/15 = 1.2. Thus, the total score for this example will be the sum of the remaining 5 boxes multiplied by 1.2. The imputed number will be rounded up to the nearest 0.5. If the score from more than 1 box is not available, the CDR-SB at that visit will be considered missing.

The interpretation of CDR-SB score is presented in Table 6-2 (O'Bryant et al. 2010), with a higher score indicating a greater cognitive deficit.

Table 6-2 Dementia Severity Categories Based on CDR-SB Scores

CDR-SB Range	Staging Category
0	Normal
0.5 - 4.0	Questionable cognitive impairment
0.5 - 2.0	Questionable impairment
2.5 - 4.0	Very mild dementia
4.5 - 9.0	Mild dementia
9.5 - 15.5	Moderate dementia
16.0 - 18.0	Severe dementia

6.4.1.1 Main Estimand for Efficacy

- Treatment condition: Group T-T (AL002 15 mg/kg, 40 mg/kg or 60 mg/kg IV Q4W) continues their Core study treatment in the LTE Study; whereas Group P-TC treated with Placebo in the Core study will be titrated up to 60 mg/kg of AL002 in the LTE study.
- Target population: adult participants with AD excluding APOE e4/e4 participants.
- Efficacy endpoint: CFB in CDR-SB.
- Accounting for intercurrent events: a composite strategy will be used to handle intercurrent events as below:
    - Hypothetical strategy for handling premature study drug discontinuation for any reason (data will be considered missing after a participant prematurely discontinued study drug plus 37 days).
    - Treatment policy strategy for handling all other intercurrent events.
- Population-level summary: the percent reduction relative to placebo decline (the proportional treatment effect), comparing each dose level to placebo.

6.4.1.2 Supportive Estimand for Efficacy

The supportive estimand is defined with the same attributes as in the main estimand for efficacy, except that a treatment policy strategy will be used to handle all intercurrent events, except death. All on-study data will be included regardless of whether an intercurrent event occurs or not. The hypothetical strategy will be used for handling death.

Another supportive estimand for the primary efficacy endpoint is defined with the same attributes as the main estimand for efficacy, except that the population-level summary is the CFB in CDR-SB to Week 24, 48, 72 and 96, comparing each dose level to placebo.

6.4.2 Other Efficacy Endpoints

The other exploratory efficacy endpoints which apply to the main estimand for efficacy endpoints include:

- CFB in MMSE
- CFB in RBANS
- CFB in ADAS-Cog13
- CFB in ADCS-ADL-MCI
- CFB in ADCOMS
- CFB in modified iADRS.

6.4.2.1 Mini-Mental Status Examination (MMSE)

The MMSE (Folstein, Folstein, and McHugh 1975) is a brief test used to measure cognitive impairment with a lower score indicating a greater cognitive deficit. The total possible score of the MMSE is 30 points and it assesses orientation (time and place), registration, attention and calculation, recent memory, language (naming, comprehension, and repetition), and constructional praxis (copying a figure).

Missing MMSE items are considered missing not at random and in a study by Godin, Keefe, and Andrew 2017, those who were missing at least one item had lower levels of cognitive function compared to those who completed all items. If only 2 or fewer items (out of 11) are missing for the MMSE, the sum of non-missing raw score of all available items will be used as the MMSE score. If more than 2 items of the MMSE are not available, the MMSE at that visit will be considered missing.

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

The RBANS used for this study is the updated version of the original RBANS (Randolph 2012) and is a collection of 12 subtests representing 5 neurocognitive domains: immediate memory, visuospatial/constructional, language, attention, and delayed memory. The raw scores from each subtest within a domain are converted to a summary score, or index score, for the domain by consulting normative data tables. Then the sum of index scores across the 5 domains is converted to a total scale that summarizes the participant's overall level of performance on this measure. The total scale score can range from 40 to 160 with a lower score indicating a greater cognitive deficit. The total scale score will be used for analysis. If any domain's index score is missing, then the total scale score will be missing.

6.4.2.3 Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog13)

The ADAS-Cog13 includes 13 items assessing cognitive function with a higher score indicating a greater cognitive deficit. The instrument includes domains for memory, language, praxis, and orientation, as well as a number cancellation task and a delayed free recall task. The ADAS-Cog13 total score is defined as the sum of the individual 13 item scores, not including the individual Trials (Trials 1, 2 and 3) for the Word Recall Task.

For the ADAS-Cog13, if 4 or fewer of a total of 13 items are missing, the total score (maximum = 85) will be imputed as follows: the total from the remaining items will be multiplied by a factor that includes the maximum score for the missing items. For example, if the first item, "Word-Recall Task," which ranges from a score of 0 through 10 (maximum = 10), is missing, and the second item "Commands,"

which ranges from a score of 0 to 5 (maximum = 5), is missing, then the multiplication factor = 85 / (85 - (10 + 5)) = 85 / 70 = 1.21. Thus, the total score for this example will be the sum of the remaining 11 items multiplied by 1.21. The imputed number will be rounded up to the nearest integer. If more than 4 items are missing, the total score of ADAS-Cog13 at that visit will be considered missing.

6.4.2.4 Alzheimer's Disease Cooperative Study – Activities of Daily Living – Mild Cognitive Impairment (ADCS-ADL-MCI)

The ADCS-ADL-MCI (Galasko et al. 1997) is a functional evaluation scale for MCI participants, based on the information provided by an informant/caregiver, that describes the performance of participants in several activities of daily living. It was adapted from the original ADCS/ADL scale, which was constructed to evaluate participants with dementia in the ADCS, as a measure of the AD participants' performance in ADL.

The ADCS-ADL-MCI is a multiple-choice questionnaire that clinicians may use to provide an assessment of mild cognitive impairment. It consists of 24 items, each answered "Yes", "No" or "Don't Know". If the respondent answers "Yes", there are sub questions that are either answered "Yes" or "No", rated on a numeric scale (which differs from question to question), or the respondent is asked to choose multiple items from a list. Only the first eighteen questions are included in the scoring.

The total score of ADCS-ADL-MCI is the summation of these response scales. The total score of ADCS-ADL-MCI ranges from 0 to 53, with a lower score indicating greater impairment.

For the ADCS-ADL-MCI, if 4 or fewer of a total of 18 items are missing, the total score will be imputed by a similar algorithm as that for the ADAS-Cog 13. The imputed value will be rounded up to the nearest integer. If more than 4 items are missing, the total score for ADCS-ADL-MCI at that visit will be considered missing. For each question, an answer of "No" or "Don't Know" will be coded to a value of 0 and is not considered as missing.

6.4.2.5 Alzheimer's Disease Composite Score (ADCOMS)

ADCOMS (J. Wang et al. 2016), a composite score, is a weighted linear combination of 12 components/items in Wold's partial least regression (PLS) model using the corresponding PLS coefficients in the fitted model (Table 6-3) and has shown improved sensitivity to clinical decline in early AD dementia populations. The 12 components/items contributing to the ADCOMS include 4 items of the ADAS-Cog13; 2 items of the MMSE, and all 6 items of the CDR-SB (Table 6-3).

The ADCOMS will be scored for each participant using the components/items and their PLS coefficients in Table 6-3, with MMSE scored in reverse (i.e., item maximum score minus measured score). The range of ADCOMS is between 0 and 1.97 and a higher score is indicative of a greater impairment on all scales.

The ADCOMS will first be calculated based on all the components/items collected on the same day. And this day will be used as the study day for the ADCOMS. If any of the items has a missing value on the same day, then the ADCOMS is set to missing for that day. If the ADCOMS can't be obtained within an analysis visit because not all components/items have non-missing values on the same day, then the ADCOMS will be calculated based on the non-missing values of components/items within the same analysis visit. And the maximum study day over all components used to calculate the ADCOMS will be used as the study day for the ADCOMS.

For the selection of data in the event of multiple records within an analysis visit for either components/items (that contribute to the composite score) or the composite score, please refer to Section 7.1.3.

*ADCOMS = A4*0.008 + A7*0.017 + A8*0.004 + A11*0.016 + (5-M1)*0.042 + (1-M7)*0.038 + C1*0.054 + C2*0.109 + C3*0.089 + C4*0.069 + C5*0.059 + C6*0.078*

Table 6-3 Items Included in ADCOMS and their Corresponding PLS Weight Coefficients

Scale	Item Name	Item ID	PLS Coefficients
ADAS-Cog13	Delayed word recall	A4	0.008
	Orientation	A7	0.017
	Word recognition	A8	0.004
	Word finding difficulty	A11	0.016
MMSE [a]	Orientation time	M1	0.042
	Drawing	M7	0.038
CDR-SB	Personal care	C1	0.054
	Community affairs	C2	0.109
	Home and hobbies	C3	0.089
	Judgement and problem solving	C4	0.069
	Memory	C5	0.059
	Orientation	C6	0.078

[a] MMSE are scored in reverse (i.e., item maximum score minus measured score).

6.4.2.6 Modified Integrated Alzheimer's Disease Rating Scale (iADRS)

The iADRS is a composite tool that combines scores from the ADAS-Cog and the AD Cooperative Study - instrumental Activities of Daily Living (ADCS-iADL) (Wessels 2015 and Wessels 2018). It demonstrates acceptable psychometric properties and is effective in capturing both disease progression and separation of placebo and active drug effect.

In this study, the modified iADRS combines scores from the ADAS-Cog13 and the ADCS-ADL-MCI. The modified iADRS score is calculated as follows:

Modified iADRS Score = [–1(ADAS-Cog13) + 85] + ADCS-ADL-MCI

The modified iADRS score will first be calculated based on the total scores of ADAS-Cog13 and ADCS-ADL-MCI of the same day; after imputation if there are missing components for either the ADAS-Cog13 or the ADCS-ADL-MCI (see rules in their respective sections above). And this day will be used as the study day for the modified iADRS score. If either the total score of ADAS-Cog13 or the total score of ADCS-ADL-MCI is missing on a day, the modified iADRS score will be considered missing on that day. If the modified iADRS score can't be obtained within an analysis visit because the total score of ADAS-Cog13 and the total score of ADCS-ADL-MCI do not have non-missing values on the same day, then the modified iADRS score will be calculated based on the non-missing values of the total score of ADAS-

Cog13 and the total score of ADCS-ADL-MCI within the same analysis visit. The maximum day of the two contributing components will be used as the study day for the modified iADRS score.

For the selection of data in the event of multiple records within an analysis visit for either component that contributes to the composite score, please refer to Section 7.1.3.

6.5 Exploratory PD Biomarker Endpoints

- CFBs in levels of sTREM2 in CSF and/or plasma
- CFBs in levels of biomarkers related to microglia function in CSF and/or plasma including but not limited to CSF1R, IL1RN, osteopontin, and YKL-40
- CFBs in levels of biomarkers related to AD pathology in CSF and/or plasma including but not limited to Aβ40, Aβ42, pTau, and tTau
- CFBs in levels of neurodegeneration biomarkers in plasma and CSF including but not limited to NfL
- CFBs in brain volume, assessed by volumetric MRI
- CFBs in brain pathological tau burden as assessed by longitudinal Tau PET scanning (for participants who agree to participate in the optional assessment only)
- CFBs in brain amyloid burden as assessed by longitudinal Amyloid PET scanning (for participants who agree to participate in the optional assessment only)

6.6 Immunogenicity Endpoints

- Incidence of ADAs
- Titers of ADAs.

7. STATISTICAL ANALYSIS

7.1 General Data Handling Rules and Definitions

"AL002 40 and 60 mg/kg combined group" refers to the group pooling AL002 40 mg/kg and 60 mg/kg treatment groups. And "AL002 total" refers to the group pooling AL002 15 mg/kg, 40 mg/kg, and 60 mg/kg, and the TC treatment groups.

Assessments collected in the Core and LTE Study that will be provided in by-participant data listings are specified in each respective section. If any dosed participant is found to not have valid documented informed consent, that participant's data will be excluded from the report, except as necessary to document the error. By-participant data listings will be presented for data collected in the Core and LTE Study for all participants and sorted by treatment group, participant identification (ID) number, visit date, and time (if applicable), unless otherwise specified. Data collected on log forms, such as AEs, will be presented in chronological order for each participant. Age at time of informed consent in the LTE Study, sex at birth, race, and ethnicity will be included in the listings.

Analyses (including analysis sets that analyses will be conducted on) to be performed for each interim analysis (IA) are specified in Section 8.

All analyses will be conducted using SAS® version 9.4 or later.

Except where specified, all continuous variables will be summarized with descriptive statistics (the number of non-missing values, mean, standard deviation (SD), median, 25% quartile (Q1), 75% quartile (Q3), minimum (min) and maximum (max)) and all categorical variables will be summarized with frequency counts and percentages, by treatment group.

Missing data will be assumed as missing at random (MAR) for all analyses and will not be imputed, unless otherwise specified.

7.1.1 Study Day and Visit Window Definitions

7.1.1.1 Study Day

The first date on which participant receives study drug (or study treatment – AL002 or placebo) per the records with non-missing dates and non-missing volume administered in the dataset corresponding to the Exposure – IV electronic CRF in the Core Study will be designated as **Core Study Day 1**. Similarly, the first day of AL002 treatment in the LTE Study will be designated as **LTE Study Day 1**. Study days for other visits will be calculated as follow:

- Before Core Study Day 1: Core Study Day = date of assessment – date of Core Study Day 1.
- On or after Core Study Day 1: Core Study Day = date of assessment – date of Core Study Day 1 + 1.
- Before LTE Day 1: LTE Study Day = date of assessment – date of LTE Study Day 1.
- On or after LTE Day 1: LTE Study Day = date of assessment – date of LTE Study Day 1 + 1.

Core Study Days continue when participants enroll in the LTE Study and are applicable to both Group T-T and Group P-TC. LTE Study Days are only applicable to Group P-TC.

7.1.1.2 Analysis Visit Window Definitions

In LTE and Integrated Analyses, analysis visit windows based on Core Study Day and LTE Study Day will both be implemented.

7.1.1.2.1 *Safety and Pharmacokinetic Data*

Unless otherwise specified, for safety and PK data, the upper bound of a post-baseline analysis visit (except for ">90 Days Post Last Dose") is the earlier date of specified upper limit and the last dose date of study drug plus 90 days. All safety and PK data that were collected beyond the last dose date of study drug plus 90 days will be assigned the analysis visit window ">90 Days Post Last Dose".

Safety and PK data will be summarized based on the analysis visits excluding ">90 Days Post Last Dose" (hereinafter may be referred to as "visit"), when applicable. Safety and PK data with ">90 Days Post Last Dose" analysis visit window will only be listed.

Safety and PK data will be allocated to analysis visits corresponding to the analysis visit window intervals in which they fall in as specified in **Error! Not a valid bookmark self-reference.** to Table 7-25.

For safety data, the analysis visits will be displayed in the format of "Week x". For Group T-T, "Week x" refers to the analysis visits based on Core Study Day. For the Placebo Data of Group P-TC, as defined in Section 3.2, "Week x" refers to the analysis visits based on Core Study Day; and for the TC Data as defined in Section 3.2, "LTE Week x" based on LTE Study Day will be abbreviated and displayed as "Week x".

Table 7-1. Analysis Visit Windows for C-SSRS Assessments Based on Core Study Day [a]

Analysis Visit	Target Day	T-T Analysis Visit Window	Placebo Analysis Visit Window[b]
Core Baseline	1	≤ 1	≤ 1
Week 24	169	[2, 253]	[2, 253]
Week 48	337	[254, 421]	[254, min (421, LTE Day 1)]
Week 72	505	[422, 533]	[422, min (533, LTE Day 1)]
Week 80	561	[534, 617]	[534, min (617, LTE Day 1)]
Week 96	673	[618, 687]	[618, min (687, LTE Day 1)]
Week 100	701	[688,715]	[688, LTE Day 1]
Week 104	729	[716, 743]	
Week 108	757	[744, 771]	
Week 112	785	[772, 799]	
Week 116	813	[800, 827]	
Week 120	841	[828, 855]	
Week 124	869	[856, 883]	
Week 128	897	[884, 911]	

DocUUID : 7f778de0-046e-479d-bb51-d30ce4769ceb

Analysis Visit	Target Day	T-T Analysis Visit Window	Placebo Analysis Visit Window[b]
Week 132	925	[912, 939]	
Week 136	953	[940, 967]	
Week 140	981	[968, 995]	
Week 144	1009	[996, 1023]	
Week 148	1037	[1024, 1065]	
Week 156	1093	> 1065	

[a] Target Day and Core Study Day are based on Core Study Day 1.
[b] LTE Day 1 represents Core Study Day of date of LTE Study Day 1. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit.

Table 7-2. Analysis Visit Windows for C-SSRS Assessments Based on LTE Study Day [a]

Analysis Visit	Target Day	Analysis Visit Window
LTE Baseline	1	≤ 1
LTE Week 4	29	[2, 43]
LTE Week 8	57	[43, 71]
LTE Week 12	85	[72, 99]
LTE Week 16	113	[100, 127]
LTE Week 20	141	[128, 155]
LTE Week 24	169	[156, 183]
LTE Week 28	197	[184, 211]
LTE Week 32	225	[212, 239]
LTE Week 36	253	[240, 267]
LTE Week 40	281	[268, 295]
LTE Week 44	309	[296, 323]
LTE Week 48	337	[324, 365]
LTE Week 56	393	> 365

[a] Target Day and LTE Study Day are based on LTE Study Day 1, unless indicated otherwise.

Table 7-3. Analysis Visit Windows for Hematology, Chemistry and Urinalysis Assessments Based on Core Study Day [a]

Analysis Visit		Target Day	T-T Analysis Visit Window	Placebo Analysis Visit Window[b]
Core Baseline		-	≤ 1	≤ 1
Week 2		15	[2, 22]	[2, 22]
Week 4		29	[23, 36]	[23, 36]
Week 6		43	[37, 64]	[37, 64]
Week 12 (Hematology and Chemistry only)		85	[65, 141]	[65, 141]
Week 28	Hematology and Chemistry	197	[142, 239]	[142, 239]
	Urinalysis		[65, 323]	[65, 323]
Week 40 (Hematology and Chemistry only)		281	[240, 323]	[240, min (323, LTE Day 1)]
Week 52		365	[324, 463]	[324, min (463, LTE Day 1)]
Week 80		561	[464,617]	[464, min (617, LTE Day 1)]
Week 96		673	[618, 687]	[618, min (687, LTE Day 1)]
Week 100		701	[688, 743]	[688, LTE Day 1]
Week 112 (Hematology and Chemistry only)		785	[744, 841]	
Week 128	Hematology and Chemistry	897	[842, 939]	
	Urinalysis		[744, 1037]	
Week 140 (Hematology and Chemistry only)		981	[940, 1037]	
Week 156		1093	> 1037	

[a] Target Day and Core Study Day are based on Core Study Day 1.
[b] LTE Day 1 represents Core Study Day of date of LTE Study Date 1. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit.

Table 7-4. Analysis Visit Windows for Hematology, Chemistry and Urinalysis Assessments Based on LTE Study Day [a]

Analysis Visit		Target Day	Analysis Visit Window
LTE Baseline		1	≤ 1
LTE Week 12 (Hematology and Chemistry only)		85	[2, 141]
LTE Week 28	Hematology and Chemistry	197	[142, 239]
	Urinalysis		[2, 337]
LTE Week 40 (Hematology and Chemistry only)		281	[240, 337]
LTE Week 56		393	> 337

[a] Target Day and LTE Study Day are based on LTE Study Day 1.

Table 7-5. Analysis Visit Windows for Coagulation Assessments Based on Core Study Day [a]

Analysis Visit	Target Day	T-T Analysis Visit Window	Placebo Analysis Visit Window[b]
Core Baseline	-	≤ 1	≤ 1
Week 4	29	[2, 169]	[2, 169]
Week 44	309	[170, 393]	[170, min (393, LTE Day 1)]
Week 68	477	[394, 575]	[394, min (575, LTE Day 1)]
Week 96	673	[576, 687]	[576, min (687, LTE Day 1)]
Week 100	701	[688, 897]	[688, LTE Day 1]
Week 156	1093	> 897	

[a] Target Day and Core Study Day are based on Core Study Day 1.
[b] LTE Day 1 represents Core Study Day of first dose date of LTE Study. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit.

Table 7-6. Analysis Visit Windows for Coagulation Assessments Based on LTE Study Day [a]

Analysis Visit	Target Day	Analysis Visit Window
LTE Baseline	1	≤ 1
LTE Week 56	393	> 1

[a] Target Day and LTE Study Day are based on LTE Study Day 1.

Table 7-7. Analysis Visit Windows for ECG Assessments Based on Core Study Day [a]

Analysis Visit [b]	Target Day	T-T Analysis Visit Window	Placebo Analysis Visit Window[c]
Core Baseline	-	≤ Day 1 Predose	≤ Day 1 Predose
Day 1 Postdose	1	Day 1 Postdose	Day 1 Postdose
Week 4	29	[2, 57]	[2, 57]
Week 12	85	[58, 127]	[58, 127]
Week 24	169	[128, 253]	[128, 253]
Week 48	337	[254, 449]	[254, min (449, LTE Day1)]
Week 80	561	[450, 617]	[450, min (617, LTE Day 1)]
Week 96	673	[618, 687]	[618, min (687, LTE Day 1)]
Week 100	701	[688, 715]	[688, LTE Day 1]
Week 104	729	[716, 757]	
Week 112	785	[758, 827]	
Week 124	869	[828, 953]	
Week 148	1037	[954, 1065]	
Week 156	1093	> 1065	

[a] Target Day and Core Study Day are based on Core Study Day 1.
[b] When assigning an analysis visit, also assign relative time as Predose or Post-infusion, which should correspond to Predose or Post-infusion as specified in Section 7.1.4.2.
[c] LTE Day 1 represents Core Study Day of first dose date of LTE Study. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit.

Table 7-8. Analysis Visit Windows for ECG Assessments Based on LTE Study Day [a]

Analysis Visit [b]	Target Day	Analysis Visit Window
LTE Baseline	1	≤ 1
LTE Week 4	29	[2, 57]
LTE Week 12	85	[58, 127]
LTE Week 24	169	[128, 253]
LTE Week 48	337	[254, 365]
LTE Week 56	393	> 365

[a] Target Day and LTE Study Day are based on LTE Study Day 1.
[b] When assigning an analysis visit, also assign relative time as Predose or Post-infusion, which should correspond to Predose or Post-infusion as specified in Section 7.1.4.2.

Table 7-9. Analysis Visit Windows for Weight Based on Core Study Day [a]

Analysis Visit	Target Day	T-T Analysis Visit Window	Placebo Analysis Visit Window[b]
Core Baseline	-	≤ 1	≤ 1
Week 4	29	[2, 43]	[2, 43]
Week 8	57	[44, 71]	[44, 71]
Week 12	85	[72, 99]	[72, 99]
Week 16	113	[100, 127]	[100, 127]
Week 20	141	[128, 155]	[128, 155]
Week 24	169	[156, 183]	[156, 183]
Week 28	197	[184, 211]	[184, 211]
Week 32	225	[212, 239]	[212, 239]
Week 36	253	[240, 267]	[240, 267]
Week 40	281	[268, 295]	[268, 295]
Week 44	309	[296, 323]	[296, 323]
Week 48	337	[324, 351]	[324, min (351, LTE Day 1)]
Week 52	365	[352, 379]	[352, min (379, LTE Day 1)]
Week 56	393	[380, 407]	[380, min (407, LTE Day 1)]
Week 60	421	[408, 435]	[408, min (435, LTE Day 1)]
Week 64	449	[436, 463]	[436, min (463, LTE Day 1)]
Week 68	477	[464, 491]	[464, min (491, LTE Day 1)]
Week 72	505	[492, 519]	[492, min (519, LTE Day 1)]
Week 76	533	[520, 547]	[520, min (547, LTE Day 1)]
Week 80	561	[548, 575]	[548, min (575, LTE Day 1)]
Week 84	589	[576, 603]	[576, min (603, LTE Day 1)]
Week 88	617	[604, 631]	[604, min (631, LTE Day 1)]
Week 92	645	[632, 659]	[632, min (659, LTE Day 1)]
Week 96	673	[660, 687]	[660, min (687, LTE Day 1)]
Week 100	701	[688,715]	[688, LTE Day 1]
Week 104	729	[716, 743]	
Week 108	757	[744, 771]	
Week 112	785	[772, 799]	
Week 116	813	[800, 827]	
Week 120	841	[828, 855]	
Week 124	869	[856, 883]	

Analysis Visit	Target Day	T-T Analysis Visit Window	Placebo Analysis Visit Window[b]
Week 128	897	[884, 911]	
Week 132	925	[912, 939]	
Week 136	953	[940, 967]	
Week 140	981	[968, 995]	
Week 144	1009	[996, 1023]	
Week 148	1037	[1024, 1065]	
Week 156	1093	> 1065	

[a] Target Day and Core Study Day are based on Core Study Day 1.
[b] LTE Day 1 represents Core Study Day of first dose date of LTE Study. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit.

Table 7-10. Analysis Visit Windows for Vital Signs Based on Core Study Day [a]

Analysis Visit[b]	Target Day	T-T Analysis Visit Window	Placebo Analysis Visit Window[c]
Core Baseline	-	≤ Day 1 Predose	≤ Day 1 Predose
Day 1 Postdose	1	Day 1 Postdose	Day 1 Postdose
Week 2	15	[2, 22]	[2, 22]
Week 4	29	[23, 36]	[23, 36]
Week 6	43	[37, 50]	[37, 50]
Week 8	57	[51, 71]	[51, 71]
Week 12	85	[72, 99]	[72, 99]
Week 16	113	[100, 127]	[100, 127]
Week 20	141	[128, 155]	[128, 155]
Week 24	169	[156, 183]	[156, 183]
Week 28	197	[184, 211]	[184, 211]
Week 32	225	[212, 239]	[212, 239]
Week 36	253	[240, 267]	[240, 267]
Week 40	281	[268, 295]	[268, 295]
Week 44	309	[296, 323]	[296, 323]
Week 48	337	[324, 351]	[324, min (351, LTE Day 1)]
Week 52	365	[352, 379]	[352, min (379, LTE Day 1)]
Week 56	393	[380, 407]	[380, min (407, LTE Day 1)]
Week 60	421	[408, 435]	[408, min (435, LTE Day 1)]
Week 64	449	[436, 463]	[436, min (463, LTE Day 1)]
Week 68	477	[464, 491]	[464, min (491, LTE Day 1)]

Analysis Visit[b]	Target Day	T-T Analysis Visit Window	Placebo Analysis Visit Window[c]
Week 72	505	[492, 519]	[492, min (519, LTE Day 1)]
Week 76	533	[520, 547]	[520, min (547, LTE Day 1)]
Week 80	561	[548, 575]	[548, min (575, LTE Day 1)]
Week 84	589	[576, 603]	[576, min (603, LTE Day 1)]
Week 88	617	[604, 631]	[604, min (631, LTE Day 1)]
Week 92	645	[632, 659]	[632, min (659, LTE Day 1)]
Week 96	673	[660, 687]	[660, min (687, LTE Day 1)]
Week 100	701	[688,715]	[688, LTE Day 1]
Week 104	729	[716, 743]	
Week 108	757	[744, 771]	
Week 112	785	[772, 799]	
Week 116	813	[800, 827]	
Week 120	841	[828, 855]	
Week 124	869	[856, 883]	
Week 128	897	[884, 911]	
Week 132	925	[912, 939]	
Week 136	953	[940, 967]	
Week 140	981	[968, 995]	
Week 144	1009	[996, 1023]	
Week 148	1037	[1024, 1065]	
Week 156	1093	> 1065	

[a] Target Day and Core Study Day are based on Core Study Day 1.
[b] When assigning an analysis visit window, also assign relative time as Predose or Post-infusion, which should correspond to Predose or Post-infusion specified in Section 7.1.4.2.
[c] LTE Day 1 represents Core Study Day of first dose date of LTE Study. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit.

Table 7-11. Analysis Visit Windows for Weight and Vital Signs Based on LTE Study Day [a]

Analysis Visit	Targeted Day	Analysis Visit Window
LTE Baseline	1	≤ 1
LTE Week 4	29	[2, 43]
LTE Week 8	57	[44, 71]
LTE Week 12	85	[72, 99]
LTE Week 16	113	[100, 127]
LTE Week 20	141	[128, 155]

LTE Week 24	169	[156, 183]
LTE Week 28	197	[184, 211]
LTE Week 32	225	[212, 239]
LTE Week 36	253	[240, 267]
LTE Week 40	281	[268, 295]
LTE Week 44	309	[296, 323]
LTE Week 48	337	[324, 365]
LTE Week 56	393	> 365

[a] Target Day and LTE Study Day are based on LTE Study Day 1.

Table 7-12. Analysis Visit Windows for MRI Assessments Based on Core Study Day [a]

Analysis Visit	Target Day	T-T Analysis Visit Window	P-TC Analysis Visit Window[b]
Core Baseline	-	≤ 1	≤ 1
Week 2	15	[2, 22]	[2, 22]
Week 4	29	[23, 36]	[23, 36]
Week 6	43	[37, 50]	[37, 50]
Week 8	57	[51, 71]	[51, 71]
Week 12	85	[72, 127]	[72, 127]
Week 24	169	[128, 253]	[128, 253]
Week 48	337	[254, 421]	[254, min (421, LTE Day 1)]
Week 72	505	[422, 589]	[422, min (589, LTE Day 1)]
Week 96	673	[590, 715]	[590, LTE Day 1]
Week 108	757	[716, 785]	LTE Week 8[c]
Week 116	813	[786, 841]	LTE Week 16[c]
Week 124	869	[842, 897]	LTE Week 24[c]
Week 132	925	[898, 953]	LTE Week 32[c]
Week 140	981	[954, 1037]	LTE Week 40[c]
Week 156	1093	> 1037	LTE Week 56[c]

[a] Target Day and Core Study Day are based on Core Study Day 1.
[b] LTE Day 1 represents Core Study Day of first dose date of LTE Study. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit.
[c] LTE Weeks are from Table 7-13. Mapping done only for volumetric MRI assessments, not for ARIA event results.

Table 7-13. Analysis Visit Windows for MRI Assessments Based on LTE Study Day [a]

Analysis Visit	Target Day	Analysis Visit Window
LTE Baseline	1	≤ 1
LTE Week 8	57	[2, 85]
LTE Week 16	113	[86, 141]
LTE Week 24	169	[142, 197]
LTE Week 32	225	[198, 253]
LTE Week 40	281	[254, 337]
LTE Week 56	393	> 337

[a] Target Day and LTE Study Day are based on LTE Study Day 1.

Table 7-14. Analysis Visit Windows for Ophthalmological Examination Based on Core Study Day [a]

Analysis Visit	Target Day	T-T Analysis Visit Window	Placebo Analysis Visit Window[b]
Core Baseline	-	≤ 1	≤ 1
Week 6	43	[2, 78]	[2, 78]
Week 16	113	[79, 169]	[79, 169]
Week 32	225	[170, 281]	[170, 281]
Week 48	337	[282, 421]	[282, min (421, LTE Day 1)]
Week 72	505	[422, 589]	[422, min (589, LTE Day 1)]
Week 96	673	[590, 687]	[590, min (687, LTE Day 1)]
Week 100	701	[688,757]	[688, LTE Day 1]
Week 116	813	[758, 869]	
Week 132	925	[870, 981]	
Week 148	1037	[982, 1065]	
Week 156	1093	> 1065	

[a] Target Day and Core Study Day are based on Core Study Day 1.
[b] LTE Day 1 represents Core Study Day of first dose date of LTE Study. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit.

Table 7-15. Analysis Visit Windows for Ophthalmological Examination Based on LTE Study Day [a]

Analysis Visit	Target Day	Analysis Visit Window
LTE Baseline	1	≤ 1
LTE Week 16	113	[2, 169]
LTE Week 32	225	[170, 281]
LTE Week 48	337	[282, 365]
LTE Week 56	393	> 365

[a] Target Day and LTE Study Day are based on LTE Study Day 1.

Table 7-16. Analysis Visit Windows for Neurological Examination Based on Core Study Day [a]

Analysis Visit	Target Day	T-T Analysis Visit Window	Placebo Analysis Visit Window[b]
Core Baseline	-	≤ 1	≤ 1
Week 6	43	[2, 64]	[2, 64]
Week 12	85	[65, 141]	[65, 141]
Week 28	197	[142, 281]	[142, 281]
Week 52	365	[282, 463]	[282, min (463, LTE Day 1)]
Week 80	561	[464, 617]	[464, min (617, LTE Day 1)]
Week 96	673	[618, 687]	[618, min (687, LTE Day 1)]
Week 100	701	[688, 729]	[688, LTE Day 1]
Week 108	757	[730, 785]	
Week 116	813	[786, 841]	
Week 124	869	[842, 897]	
Week 132	925	[898, 953]	
Week 140	981	[954, 1009]	
Week 148	1037	[1010, 1065]	
Week 156	1093	> 1065	

[a] Target Day and Core Study Day are based on Core Study Day 1.
[b] LTE Day 1 represents Core Study Day of first dose date of LTE Study. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit.

DocUUID : 7f778de0-046e-479d-bb51-d30ce4769ceb

Table 7-17. Analysis Visit Windows for Neurological Examination Based on LTE Study Day [a]

Analysis Visit	Target Day	Analysis Visit Window
LTE Baseline	1	≤ 1
LTE Week 8	57	[2, 85]
LTE Week 16	113	[86, 141]
LTE Week 24	169	[142, 197]
LTE Week 32	225	[198, 253]
LTE Week 40	281	[254, 309]
LTE Week 48	337	[310, 365]
LTE Week 56	393	> 365

[a] Target Day and LTE Study Day are based on LTE Study Day 1.

Table 7-18. Analysis Visit Windows for Physical Examination Based on Core Study Day [a]

Analysis Visit	Target Day	T-T Analysis Visit Window	Placebo Analysis Visit Window[b]
Core Baseline	-	≤ 1	≤ 1
Week 12	85	[2, 141]	[2, 141]
Week 28	197	[142, 281]	[142, 281]
Week 52	365	[282, 463]	[282, min (463, LTE Day 1)]
Week 80	561	[464, 617]	[464, min (617, LTE Day 1)]
Week 96	673	[618, 687]	[618, min (687, LTE Day 1)]
Week 100	701	[688, 743]	[688, LTE Day 1]
Week 112	785	[744, 841]	
Week 128	897	[842, 995]	
Week 156	1093	> 995	

[a] Target Day and Core Study Day are based on Core Study Day 1.
[b] LTE Day 1 represents Core Study Day of first dose date of LTE Study. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit.

Table 7-19. Analysis Visit Windows for Physical Examination Based on LTE Study Day [a]

Analysis Visit	Target Day	Analysis Visit Window
LTE Baseline	1	≤ 1
LTE Week 12	85	[2, 141]
LTE Week 28	197	[142, 295]
LTE Week 56	393	> 295

[a] Target Day and LTE Study Day are based on LTE Study Day 1.

Table 7-20. Analysis Visit Windows for ADA (Serum) Assessments Based on Core Study Day [a]

Analysis Visit	Target Day	T-T Analysis Visit Window	Placebo Analysis Visit Window[b]
Core Baseline	-	≤ 1	≤ 1
Week 2	15	[2, 22]	[2, 22]
Week 4	29	[23, 36]	[23, 36]
Week 6	43	[37, 50]	[37, 50]
Week 8	57	[51, 85]	[51, 85]
Week 16	113	[86, 141]	[86, 141]
Week 24	169	[142, 211]	[142, 211]
Week 36	253	[212, 295]	[212, 295]
Week 48	337	[296, 379]	[296, min (379, LTE Day 1)]
Week 60	421	[380, 463]	[380, min (463, LTE Day 1)]
Week 72	505	[464, 547]	[464, min (547, LTE Day 1)]
Week 84	589	[548, 631]	[548, min (631, LTE Day 1)]
Week 96	673	[632, 687]	[632, min (687, LTE Day 1)]
Week 100	701	[688, 715]	[688, LTE Day 1]
Week 104	729	[716, 743]	
Week 108	757	[744, 785]	
Week 116	813	[786, 841]	
Week 124	869	[842, 911]	
Week 136	953	[912, 995]	
Week 148	1037	[996, 1065]	
Week 156	1093	> 1065	

[a] Target Day and Core Study Day are based on Core Study Day 1.
[b] LTE Day 1 represents Core Study Day of first dose date of LTE Study. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit.

Table 7-21. Analysis Visit Windows for ADA (Serum) Assessments Based on LTE Study Day [a]

Analysis Visit	Target Day	Analysis Visit Window
LTE Baseline	1	≤ 1
LTE Week 4	29	[2, 43]
LTE Week 8	57	[44, 85]
LTE Week 16	113	[86, 141]

LTE Week 24	169	[142, 211]
LTE Week 36	253	[212, 295]
LTE Week 48	337	[296, 365]
LTE Week 56	393	> 365

[a] Target Day and LTE Study Day are based on LTE Study Day 1.

Table 7-22. Analysis Visit Windows for PK (Serum) Assessments Based on Core Study Day [a]

Analysis Visit	Target Day	T-T Analysis Visit Window	Placebo Analysis Visit Window[b]
Day 1	1	≤ 1	≤ 1
Week 1	8	[2, 12]	[2, 12]
Week 2	15	[13, 22]	[13, 22]
Week 4	29	[23, 36]	[23, 36]
Week 6	43	[37, 50]	[37, 50]
Week 8	57	[51, 71]	[51, 71]
Week 12	85	[72, 99]	[72, 99]
Week 16	113	[100, 141]	[100, 141]
Week 24	169	[142, 211]	[142, 211]
Week 36	253	[212, 295]	[212, 295]
Week 48	337	[296, 351]	[296, min (351, LTE Day 1)]
Week 52	365	[352, 379]	[352, min (379, LTE Day 1)]
Week 56	393	[380, 407]	[380, min (407, LTE Day 1)]
Week 60	421	[408, 435]	[408, min (435, LTE Day 1)]
Week 64	449	[436, 463]	[436, min (463, LTE Day 1)]
Week 68	477	[464, 491]	[464, min (491, LTE Day 1)]
Week 72	505	[492, 519]	[492, min (519, LTE Day 1)]
Week 76	533	[520, 547]	[520, min (547, LTE Day 1)]
Week 80	561	[548, 575]	[548, min (575, LTE Day 1)]
Week 84	589	[576, 603]	[576, min (603, LTE Day 1)]
Week 88	617	[604, 631]	[604, min (631, LTE Day 1)]
Week 92	645	[632, 659]	[632, min (659, LTE Day 1)]
Week 96	673	[660, 687]	[660, min (687, LTE Day 1)]
Week 100	701	[688,715]	[688, LTE Day 1]
Week 104	729	[716, 743]	
Week 108	757	[744, 785]	

Week 116	813	[786, 841]	
Week 124	869	[842, 911]	
Week 136	953	[912, 995]	
Week 148	1037	[996, 1065]	
Week 156	1093	> 1065	

[a] Target Day and Core Study Day are based on Core Study Day 1.
[b] LTE Day 1 represents Core Study Day of first dose date of LTE Study. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit.

Table 7-23. Analysis Visit Windows for PK (Serum) Assessments Based on LTE Study Day [a]

Analysis Visit	Target Day	Analysis Visit Window
LTE Baseline	1	≤ 1
LTE Week 4	29	[2, 43]
LTE Week 8	57	[44, 85]
LTE Week 16	113	[86, 141]
LTE Week 24	169	[142, 211]
LTE Week 36	253	[212, 295]
LTE Week 48	337	[296, 365]
LTE Week 56	393	> 365

[a] Target Day and LTE Study Day are based on LTE Study Day 1.

Table 7-24. Analysis Visit Windows for PK (CSF) Assessments Based on Core Study Day [a]

Analysis Visit	Target Day	T-T Analysis Visit Window	Placebo Analysis Visit Window[b]
Core Baseline	1	≤ 1	≤ 1
Week 6	43	[2, 190]	[2, 190]
Week 48	337	[191, 421]	[191, min (421, LTE Day 1)]
Week 72	505	[422, 589]	[422, min (589, LTE Day 1)]
Week 96	673	[590, 687]	[590, min (687, LTE Day 1)]
Week 100	701	[688, 869]	[688, LTE Day 1]
Week 148	1037	> 869	

[a] Target Day and Core Study Day are based on Core Study Day 1.
[b] LTE Day 1 represents Core Study Day of first dose date of LTE Study. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit.

Table 7-25. Analysis Visit Windows for PK (CSF) Assessments Based on LTE Study Day [a]

Analysis Visit	Target Day	Analysis Visit Window
LTE Baseline	1	≤ 1

LTE Week 48	337	≥ 2

[a] Target Day and LTE Study Day are based on LTE Study Day 1.

7.1.1.2.2 *Efficacy Data*

For the efficacy endpoints, assessments will be allocated to analysis visits using the analysis visit window intervals in which they fall in as specified in Table 7-26.

Analysis visit windows for efficacy parameters are defined in a similar manner as those for safety and PK data. Efficacy data will be summarized based on the analysis visits (hereinafter may be referred to as "visit"), when applicable.

For efficacy data, the analysis visits will be in the format of "Week y/LTE Week x" when applicable, where "LTE Week x" refers to the analysis visits based on LTE Study Day for Group P-TC, "Week y" refers to the analysis visits based on Core Study Day for Group T-T (e.g. Week 104/LTE Week 4, Week 156/LTE Week 56). For data during the Core study, Group T-T and Group P-TC will have the label "Week x". For the TC, "LTE Week x" will be abbreviated and displayed as "Week x" for the TC, and shown along with "Week x" values of Group T-T.

Table 7-26. Analysis Visit Windows for Efficacy Assessments Based on Core Study Day [a]

Nominal Visit per Protocol	Target Day	Analysis Visit	T-T Analysis Visit Window	P-TC Analysis Visit Window[d]
Screening Phase		Core Baseline[c]	≤ 1	≤ 1
Screening	-			
Treatment Phase				
Week 1 [b]	1			
Week 25	169	Week 24	[2, 253]	[2, 253]
Week 49	337	Week 48	[254, 421]	[254, min (421, LTE Day 1)]
Week 73	505	Week 72	[422, 589]	[422, min (589, LTE Day 1)]
Week 97	673	Week 96	[590, 771]	[590, LTE Day 1]
Week 125	869	Week 124	[772, 953]	LTE Week 24
Week 149	1037	Week 148	> 953	LTE Week 48

[a] Target Day and Core Study Day are based on Core Study Day 1.
[b] COAs are scheduled to be performed/collected prior to dosing.
[c] Baseline for efficacy is defined in Section 7.1.2.
[d] LTE Day 1 represents Core Study Day of first dose date of LTE Study. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit. LTE Weeks are from Table 7-27.

Table 7-27. Analysis Visit Windows for Efficacy Assessments Based on LTE Study Day [a]

Nominal Visit per Protocol	Target Day	Analysis Visit	Analysis Visit Window
LTE Day 1	1	LTE Baseline	≤ 1
LTE Week 25	169	LTE Week 24	[2, 253]

LTE Week 49	337	LTE Week 48	≥ 254

[a] Target Day and LTE Study Day are based on LTE Study Day 1.

7.1.1.2.3 *Fluid (Plasma, CSF) and PET Imaging (Amyloid and Tau) Biomarker Data*

Analysis visit windows for the biomarker parameters are defined in a similar manner as those for the efficacy parameters (refer to Section 7.1.1.2.2). Biomarker data will be allocated to analysis visits corresponding to the analysis visit window intervals in which they fall in as specified in **Error! Reference source not found.** to **Error! Reference source not found.**.

Table 7-28. Analysis Visit Windows for PD Plasma Biomarker Assessments Based on Core Study Day [a]

Analysis Visit	Target Day	T-T Analysis Visit Window	P-TC Analysis Visit Window[b]
Core Baseline	1	≤ 1	≤ 1
Week 1	8	[2, 12]	[2, 12]
Week 2	15	[13, 22]	[13, 22]
Week 4	29	[23, 36]	[23, 36]
Week 6	43	[37, 50]	[37, 50]
Week 8	57	[51, 71]	[51, 71]
Week 12	85	[72, 99]	[72, 99]
Week 16	113	[100, 141]	[100, 141]
Week 24	169	[142, 211]	[142, 211]
Week 36	253	[212, 295]	[212, 295]
Week 48	337	[296, 379]	[296, min (379, LTE Day 1)]
Week 60	421	[380, 463]	[380, min (463, LTE Day 1)]
Week 72	505	[464, 547]	[464, min (547, LTE Day 1)]
Week 84	589	[548, 631]	[548, min (631, LTE Day 1)]
Week 96	673	[632, 701]	[632, LTE Day 1]
Week 104	729	[702, 743]	LTE Week 4
Week 108	757	[744, 785]	LTE Week 8
Week 116	813	[786, 841]	LTE Week 16
Week 124	869	[842, 911]	LTE Week 24
Week 136	953	[912, 995]	LTE Week 36
Week 148	1037	[996, 1065]	LTE Week 48
Week 156	1093	> 1065	LTE Week 56

[a] Target Day and Core Study Day are based on Core Study Day 1.
[b] LTE Day 1 represents Core Study Day of first dose date of LTE Study. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit. LTE Weeks are from Table 7-29.

Table 7-29. Analysis Visit Windows for PD Plasma Biomarker Assessments Based on LTE Study Day [a]

Analysis Visit	Target Day	Analysis Visit Window
LTE Baseline	1	≤ 1
LTE Week 4	29	[2, 43]
LTE Week 8	57	[44, 85]
LTE Week 16	113	[86, 141]
LTE Week 24	169	[142, 211]
LTE Week 36	253	[212, 295]
LTE Week 48	337	[296, 365]
LTE Week 56	393	> 365

[a] Target Day and LTE Study Day are based on LTE Study Day 1.

Table 7-30. Analysis Visit Windows for CSF Biomarker Assessments Based on Core Study Day [a]

Analysis Visit	Target Day	T-T Analysis Visit Window	P-TC Analysis Visit Window[b]
Core Baseline	1	≤ 1	≤ 1
Week 6	43	[2, 190]	[2, 190]
Week 48	337	[191, 421]	[191, min (421, LTE Day 1)]
Week 72	505	[422, 589]	[422, min (589, LTE Day 1)]
Week 96	673	[590, 855]	[590, LTE Day 1]
Week 148	1037	> 855	LTE Week 48

[a] Target Day and Core Study Day are based on Core Study Day 1.
[b] LTE Day 1 represents Core Study Day of first dose date of LTE Study. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit. LTE Week 48 window is any day > LTE Day 1.

Table 7-31. Analysis Visit Windows for CSF Biomarker Assessments Based on LTE Study Day [a]

Analysis Visit	Target Day	Analysis Visit Window
LTE Baseline	1	≤ 1
LTE Week 48	337	> 1

[a] Target Day and LTE Study Day are based on LTE Study Day 1.

Table 7-32. Analysis Visit Windows for Amyloid PET Assessments Based on Core Study Day [a]

Analysis Visit	Target Day	T-T Analysis Visit Window	P-TC Analysis Visit Window[b]
Core Baseline	1	≤ 1	≤ 1
Week 48	337	[2, 505]	[2, min (505, LTE Day 1)]
Week 96	673	[506, 771]	[506, LTE Day 1]

DocUUID : 7f778de0-046e-479d-bb51-d30ce4769ceb

Week 124	869	[772, 953]	LTE Week 24
Week 148	1037	> 953	LTE Week 48

[a] Target Day and Core Study Day are based on Core Study Day 1.
[b] LTE Day 1 represents Core Study Day of first dose date of LTE Study. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit. LTE Weeks are from Table 7-33.

Table 7-33. Analysis Visit Windows for Amyloid PET Assessments Based on LTE Study Day [a]

Analysis Visit	Target Day	Analysis Visit Window
LTE Baseline	1	≤ 1
LTE Week 24	169	[2, 253]
LTE Week 48	337	> 253

[a] Target Day and LTE Study Day are based on LTE Study Day 1.

Table 7-34. Analysis Visit Windows for Tau PET Assessments Based on Core Study Day [a]

Analysis Visit	Target Day	T-T Analysis Visit Window	P-TC Analysis Visit Window[b]
Core Baseline	1	≤ 1	≤ 1
Week 48	337	[2, 421]	[2, min (421, LTE Day 1)]
Week 72	505	[422, 589]	[422, min (589, LTE Day 1)]
Week 96	673	[590, 771]	[590, LTE Day 1]
Week 124	869	[772, 981]	LTE Week 24
Week 156	1093	> 981	LTE Week 56

[a] Target Day and Core Study Day are based on Core Study Day 1.
[b] LTE Day 1 represents Core Study Day of first dose date of LTE Study. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit. LTE Weeks are from Table 7-35.

Table 7-35. Analysis Visit Windows for Tau PET Assessments Based on LTE Study Day [a]

Analysis Visit	Target Day	Analysis Visit Window
LTE Baseline	1	≤ 1
LTE Week 24	169	[2, 281]
LTE Week 56	393	> 281

[a] Target Day and LTE Study Day are based on LTE Study Day 1.

Table 7-36. Analysis Visit Windows for Tau PET Assessments, Redefined Baseline [a] (Sensitivity Analysis)[b]

Analysis Visit	Target Day	T-T Analysis Visit Window	P-TC Analysis Visit Window[c]
Baseline_R	1	≤ Day 1 Predose, if it exists. If not, then first day of non-missing result (up to Day 421)	
Week_R 48	337	[2, 421]	[2, min (421, LTE Day 1)]
Week_R 72	505	[422, 589]	[422, min (589, LTE Day 1)]
Week_R 96	673	[590, 771]	[590, LTE Day 1]

Week_R 124	869	[772, 981]	LTE Week 24
Week_R 156	1093	> 981	LTE Week 56

[a] Target Day and Core Study Day are based on Core Study Day 1.
[b] Redefined baseline: baseline corresponds to either the pre-dose visit (prior to dosing) in Core Study if the pre-dose Tau PET scan is evaluable, or 1st postdose scan in Core Study if the pre-dose Tau PET scan is missing.
[c] LTE Day 1 represents Core Study Day of first dose date of LTE Study. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit. LTE Weeks are from Table 7-35.

7.1.2 Selection of Data for LTE Baseline

The LTE baseline value will be chosen based on the rules specified below, unless otherwise specified. Note that LTE Baseline is applicable only to Group P-TC, unless otherwise specified.

7.1.2.1 Measurements Without a Source Recording Measurement Time Point

The baseline value will be the last non-missing and evaluable value prior to or on LTE Study Day 1.

If multiple non-missing and evaluable records occur on the same day that is closest to LTE Study Day 1 or on LTE Study Day 1:

- For continuous measurements other than laboratory and PD biomarker data, the best of these records will be considered the baseline value.
- For continuous measurements for laboratory and PD biomarker data, the average of these records will be considered the baseline value.
- For categorical measurements regardless the type of endpoints (not applicable to categorical measurements derived from continuous measurements), the record with the lowest severity will be considered the baseline value, for example:
    - Lower grade severity will be selected over higher grade severity for toxicity grades or severity;
    - “normal” will be selected over “low” and “high” for a test or exam with those categories;
    - “normal” will be selected over “abnormal” for a test or exam with those two categories;
    - “negative” will be selected over “positive” for a test or exam with those two categories.

7.1.2.2 Measurements With a Source Recording Measurement Time Point

For measurements that have a source recording the measurement time point (e.g., the measurement time point of vital signs and ECG data are recorded on the corresponding electronic CRF; the measurement time point of sTREM2 data is recorded in the vendor data), the baseline value will be the last non-missing and evaluable value prior to LTE Study Day 1, or the last non-missing and evaluable value with “predose” missing, or “not applicable” (i.e., excluding value collected post infusion) as the measurement time point (as recorded in the source data) on LTE Study Day 1. Non-missing values with “post infusion” (or containing “end of infusion” (EOI)) as the measurement time point (as recorded in the source data) on Study Day 1 are not considered candidates for the baseline value and will be assigned the analysis visit “Day 1 Postdose” ([a] Target Day and Core Study Day are based on Core Study Day 1.
[b] LTE Day 1 represents Core Study Day of first dose date of LTE Study. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit.

Table 7-6. Analysis Visit Windows for Coagulation Assessments Based on LTE Study Day [a]

Analysis Visit	Target Day	Analysis Visit Window
LTE Baseline	1	≤ 1
LTE Week 56	393	> 1

[a] Target Day and LTE Study Day are based on LTE Study Day 1.

Table 7-7 and [a] Target Day and Core Study Day are based on Core Study Day 1.
[b] LTE Day 1 represents Core Study Day of first dose date of LTE Study. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit.

Table 7-10) when applicable.

If multiple non-missing and evaluable records occur on the same day that is closest to LTE Study Day 1 (not on LTE Study Day 1), or on LTE Study Day 1 and all with "predose", missing, or "not applicable" as the measurement time point:

- For continuous measurements, the average of these values will be considered the baseline value.
- For categorical measurements (not applicable to categorical measurements derived from continuous measurements), the record with the lowest severity will be considered the baseline value (e.g., "abnormal not clinically significant" will be selected over "abnormal clinically significant").

7.1.3 Selection of Data in the Event of Multiple Records in a Post-Baseline Analysis Visit Window

7.1.3.1 Efficacy Data

For non-composite efficacy endpoints:
If multiple valid, non-missing efficacy records exist in a post-baseline analysis visit window, records will be chosen based on the following rules if a single value is needed, unless otherwise specified:

- The record closest to the target day (in terms of days) for that visit will be selected.
- If there are multiple records that are equidistant from the target day (in terms of days), the later record will be selected.
- If there are multiple records on the same day and the chronological order (in terms of day and time) can be determined (e.g., with time known on the same day), the latest record will be selected.
- If there are multiple records on the same day and the chronological order cannot be determined (e.g., more than one record on the same day with time missing), the worst record will be selected.

For composite efficacy endpoints (ADCOMS and modified iADRS):

Refer to Section 6.4.2.5 and 6.4.2.6 for scenarios when components of composite endpoints are from different day.

If all the individual components have no multiple records on the same day, then the composite score is first calculated based on all the individual components collected on the same day. After the composite score is calculated, if multiple composite scores exist in a post-baseline analysis visit window, then:

- The record closest to the target day (in terms of days) for that visit will be selected.
- If there are multiple records that are equidistant from the target day (in terms of days), the later record will be selected.

If one or more individual components have multiple records on the same day, then the following rules of selection for those individual components apply first, followed by the rules above to calculate and select the composite score:

- If there are multiple records on the same day and the chronological order (in terms of day and time) can be determined (e.g., more than one record with time known on the same day), the latest record will be selected.
- If there are multiple records on the same day and the chronological order cannot be determined (e.g., more than one record on the same day with time missing), the worst record will be selected.

7.1.3.2 Safety and PD Biomarker Data

Depending on the statistical analysis method, a single value may be required for each analysis visit window (e.g., CFB by visit usually requires a single value), except for ">90 Days Post Last Dose" analysis visit window.

For safety data, if multiple valid, non-missing, continuous records exist in a post-baseline analysis visit window, records will be chosen based on the following rules if a single value is needed, unless otherwise specified:

- The record closest to the target day (in terms of days) for that visit will be selected.
- If there are multiple records that are equidistant from the target day (in terms of days), the later record will be selected.
- If there are multiple records on the same day (regardless of time), the average will be taken.

For exploratory PD biomarker data, if multiple valid, non-missing, continuous records exist in a post-baseline analysis visit window, then the average of these records will be taken.

For safety and exploratory PD biomarker data, if multiple valid, non-missing, categorical records exist in a post-baseline analysis visit window (not applicable to categorical measurements derived from continuous measurements), records will be chosen based on the following rules if a single value is needed, unless otherwise specified:

- The record closest to the target day for that visit (in terms of days) will be selected.
- If there are multiple records that are equidistant from the target day (in terms of days), the later record will be selected.
- If there are multiple records on the same day, the record with the worst severity will be selected, for example:
    - higher grade severity will be selected over lower grade severity for toxicity grades;
    - "low" or "high" will be selected over "normal" for a test or exam with those categories;
    - "abnormal" will be selected over "normal" for a test or exam with those two categories;
    - "positive" will be selected over "negative" for a test or exam with those two categories.

For those categorical measurements derived from continuous measurements, if multiple valid, non-missing, continuous records exist in an analysis visit window, the rules for selecting a single value for continuous measurements apply first, then the corresponding categorical measurements will be derived based on the single selected continuous measurements.

Measurements that are collected both predose and post-infusion also follow the above rules for post-baseline visits, but per each measurement time point (i.e., per predose, per post-infusion, and not applicable).

7.1.4 Data Handling Conventions and Transformations

7.1.4.1 Conversion of Categorical Values to Numerical Values

For non-PK data that are continuous in nature, certain categorical values will be converted to numerical values for calculating summary statistics. For non-PK data that are categorical in nature (i.e., all possible outcomes are categorical), no conversion from categorical values to numerical values will apply for calculating summary statistics, unless otherwise specified.

7.1.4.1.1 *Handling of LLOQ and ULOQ*

Non-PK data that are continuous in nature (e.g., safety lab tests) but are less than the LLOQ or above the ULOQ will be imputed as follows:

- A value that is 1 unit less than the LLOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LLOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used for calculating summary statistics.
- A value that is 1 unit above the ULOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the ULOQ). Values with decimal points will follow the same logic as above.
- The LLOQ or ULOQ will be used to calculate descriptive statistics if the data is reported in the form of "≤ x" or "≥ x" (where x is considered the LLOQ or ULOQ).
- "Occasional" will be assigned 1 unit less than the LLOQ. An exception to this rule is if LLOQ is 1 or 0.1, a value of 0.9 or 0.09, respectively, will be used for calculating summary statistics.

7.1.4.1.2 *Handling of Other Special Characters*

Non-PK data that are continuous in nature but have a "x – y" interval value will be imputed as best of "x – y" for baseline and worst of "x – y" for post-baseline as their continuous numeric value, if needed for calculating summary statistics.

Non-PK data that are continuous in nature but have "None" representing zero will be assigned 0, if needed for calculating summary statistics.

Non-PK data that are continuous in nature but have "ND (not done)", "QNS (quantity not sufficient)", "NR (no result(s))", or "Non-evaluable" representing non-valuable or missing value will be assigned missing, if needed for calculating summary statistics.

7.1.4.1.3 *Handling of Special Laboratory Categorical Data*

For a laboratory test that is continuous in nature but only had numeric values present when the result was abnormal but absent when the result was normal (e.g., when urine protein was normal (i.e., negative or absent), no numeric value was present in data), the numeric value will be assigned 0 corresponding to a normal (negative or absent) test result, and it is not considered as missing or unknown.

7.1.4.2 Handling of Predose and Post-infusion

For vital signs and ECG data that collect measurements at multiple time points (predose, post-infusion, or "Not Applicable") on a study drug administration day, the following rules apply for assigning the measurements to times, when applicable.

(1) For the assessments collected on Study Day 1:

- The entries on the corresponding electronic CRF (predose, post-infusion) will be used.
  - If the entry on the corresponding electronic CRF is "post-infusion", the assessment will be assigned the analysis visit "Day 1 Postdose". Measurement time points are not applicable for "Day 1 Postdose".
  - If the entry on the corresponding electronic CRF is "predose", it will be considered as a candidate for baseline, and the baseline selection rules apply. Measurement time points are not applicable for baseline.

(2) For assessments collected at a post-Study-Day-1 scheduled visit, in which study drug is administered per the Schedules of Assessments in the protocols, the entries on the corresponding electronic CRF (predose, post-infusion) will be used, if the date of assessment is prior to or on the last dose date.

(3) For post-Study-Day-1 visits at which study drug is not administered per the Schedules of Assessments in the protocols, including Week 3 (vital signs only), Unscheduled, EFU, SFU, and ET, "Not Applicable" will be assigned as the measurement time point.

(4) For assessments collected after the last dose date, "Not Applicable" will be assigned as the measurement time point. And this takes precedence over entries on the corresponding electronic CRF.

(5) For assessments collected prior to the first dose date, time points do not apply. And this takes precedence over entries on the corresponding electronic CRF.

7.1.4.3 Handling of Baseline Value being Zero

For an endpoint, the percent change from baseline (PCFB) at a post-baseline visit is calculated as follows:

$$((\text{post-baseline value} - \text{baseline value}) / \text{baseline value}) \times 100\%$$

If the baseline value is 0 and the post-baseline value is also 0, then the PCFB is set to 0. If the baseline is 0 and the post-baseline value is non-zero then the PCFB is set to missing.

7.2 Participant Disposition and Protocol Deviations

7.2.1 Participant Enrollment and Disposition

For LTE analysis using ATS-LTE, a summary of participant enrollment will be provided by individual AL002 15 mg/kg, 40 mg/kg, and 60 mg/kg, and the TC treatment groups, AL002 40 and 60 mg/kg combined group and AL002 total group for each country, as well as for each investigator within a country. The summary will present the number and percentage of participants dosed in the LTE Study. For each column, the denominator for the percentage calculation will be the total number of participants analyzed for that column.

For Integrated analysis using ATS, a summary of participant disposition will be provided by individual AL002 15 mg/kg, 40 mg/kg, and 60 mg/kg, and the placebo/TC treatment groups, AL002 40 and 60 mg/kg combined group, and AL002 total group. This summary will present the number of participants dosed in the LTE Study, and the number of dosed participants in each of the categories listed below:

- Ongoing study drug if applicable
- Completed study drug
- Discontinued study drug
- Reasons for premature discontinuation of study drug
- Ongoing study if applicable
- Completed study
- Discontinued study
- Reasons for premature discontinuation of study

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of participants in each category will be provided. The denominator for the percentage calculation for the study drug completion/discontinuation and study completion/discontinuation will be the total number of participants in the corresponding analysis set.

By-participant data listings for participant disposition will be provided.

7.2.2 Protocol Deviations

Protocol deviations will be recorded separately from the clinical database. A blinded review of the deviation log, as well as a programmatic listing of protocol deviations to determine non-significant and significant protocol deviations, will be conducted prior to final database lock. All significant deviations in the LTE Study will be summarized by individual AL002 15 mg/kg, 40 mg/kg, and 60 mg/kg, and the TC treatment groups, AL002 40 and 60 mg/kg combined group, and AL002 total group. A by-participant data listing of all significant protocol deviations including categorization of deviations, as significant or non-significant, will be provided.

7.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics specified in this section will be summarized by individual AL002 15 mg/kg, 40 mg/kg, and 60 mg/kg, and the TC treatment groups, AL002 40 and 60 mg/kg combined group, and AL002 total group.

7.3.1 Demographics, Social History, and Medical History

For LTE Analysis, demographics from the Core Study, unless updated in the LTE Study, will be summarized for the ATS-LTE. In other words, for demographics, if the value is missing from the LTE Study, the one from the Core Study will be used in its place, except for age at time of informed consent. The age at time of informed consent of the LTE Study will be summarized.

Weight, height and BMI refer to the Core baseline for Group T-T and LTE baseline for Group P-TC (refer to Section 7.1.2 for definition), and will be summarized by treatment group, AL002 40 and 60 mg/kg combined group, and overall for the ATS-LTE.

Social history, medical history, and medical and surgical treatment procedures will be listed for the LTE Analysis and the Integrated Analysis.

By-participant data listings will be presented for the ATS.

For the Integrated Analysis, demographics will be summarized as they are in the Core Study for the ATS. They will also be shown for the FAS.

7.3.2 Prior and Concomitant Medications

Concomitant medications will be summarized by ATC drug class Level 4 and preferred name using the number and percentage of participants for each treatment group, AL002 40 and 60 mg/kg combined group, and AL002 total group for the Non-e4/e4 Set.

A participant reporting the same medication more than once will be counted only once within each ATC drug class when calculating the number and percentage of participants who received that medication. Medications may appear under multiple ATC drug classes. The summary will be ordered alphabetically by ATC medical class and then by preferred name in descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

All medications (other than per-protocol study drugs) will be provided in a by-participant data listing sorted by participant ID number and administration date in chronological order.

7.4 Safety Analyses

All safety endpoints will be summarized with the Integrated Analysis, unless otherwise specified. The selected safety endpoints that will be summarized with the LTE Analysis are specified in the respective sections.

All LTE Analysis for a safety endpoint will be based on the ATS-LTE, unless otherwise specified. All Integrated Analysis for a safety endpoint will be based on the Non-e4/e4 Set, unless otherwise specified. Analysis sets are defined in Section 5.

Analyses (including analysis sets that analyses will be conducted on) to be performed for each interim analysis (IA) are specified in Section 8.

Unless otherwise specified, CFB for Group T-T and placebo will be based on the Core baseline. CFB for Titration Cohort will be based on the LTE baseline. Baseline is defined in Section 6.1. Core baseline and LTE baseline are referred to as baseline for simplicity in this section.

Analysis visit window definitions are described in Section 7.1.1.2.1.

In the case of multiple values in an analysis visit window, data will be selected for analysis as described in Section 7.1.3.2, unless otherwise specified.

7.4.1 Descriptive Summaries of Safety Endpoints

7.4.1.1 LTE Descriptive Summaries of Safety Endpoints

The LTE descriptive summary of a safety endpoint will summarize the data collected in the LTE Study (plus Core baseline when applicable) with descriptive statistics, by individual AL002 15 mg/kg, 40 mg/kg, and 60 mg/kg, and the TC treatment groups, AL002 40 and 60 mg/kg combined group, and AL002 total group.

When applicable, for a continuous safety endpoint, the number of participants with safety outcomes, mean, SD, median, Q1, Q3, min, and max, at baseline (Core baseline for Group T-T and LTE baseline for the TC (refer to Section 7.1.2 for baseline definition)) and each analysis visit (based on Core Study Day for Group T-T and based on LTE Study Day for the TC), along with the CFB at each analysis visit, will be summarized.

The CFB for Group T-T will be based on the Core baseline, and the CFB for the TC will be based on the LTE baseline. And only analysis visits occurring in the LTE Study are included in the LTE Analyses.

By-participant data listings for safety data will be provided.

7.4.1.2 Integrated Descriptive Summaries of Safety Endpoints

The integrated descriptive summary of a safety endpoint including the Placebo Data will summarize all the data collected in the Core Study and in the LTE Study with descriptive statistics based on the Non-e4/e4 Set, by individual placebo, AL002 15 mg/kg, 40 mg/kg, and 60 mg/kg, and the TC treatment groups, AL002 40 and 60 mg/kg combined group, and AL002 total group.

The CFB will be based on the Core baseline for placebo, AL002 15 mg/kg, 40 mg/kg, and 60 mg/kg, and AL002 40 and 60 mg/kg combined treatment groups. The CFB for the TC will be based on the LTE baseline. And all analysis visits from the Core and LTE Studies will be included.

7.4.1.2.1 *Integrated Descriptive Summaries of Safety Endpoints by Time Interval of Events Occurrence*

Selected safety endpoints (as specified in Section 8) will be summarized by the categories of timing to occurrence of events since Core Study Day 1 (for Group T-T and placebo) or LTE Study Day 1 (for the Titration Cohort) in weeks: < 48 Weeks, ≥ 48 – < 96 Weeks, ≥ 96 – < 144 Weeks, and ≥ 144 Weeks. Timing to occurrence of events since Core Study Day 1 (for Group T-T and placebo) or LTE Study Day 1 (for the Titration Cohort) in weeks is calculated as the number of weeks between the Core/LTE Study Day 1 and event start date, i.e., timing to occurrence of events = (event start date - Core/LTE Study Day 1 + 1) / 7. In the event of missing or incomplete event start date, the same imputation rules as specified for the events apply.

7.4.2 Extent of Exposure to AL002

Duration of exposure to AL002, the total number of AL002 doses received, and treatment compliance as defined in Section 6.2.1 will be summarized by treatment group, AL002 40 and 60 mg/kg combined group, and overall.

Duration of exposure to AL002 will be summarized in days, weeks, months, and participant-years of exposure for both the LTE Analysis and the Integrated Analysis.

The total number of study drug doses received will be summarized as a continuous measure for both the LTE Analysis and the Integrated Analysis.

For the LTE Analysis, duration of LTE exposure to AL002 as specified in Section 6.2.1 and the total number of AL002 doses received will summarize the study drug administration of AL002 collected in the LTE Study. And duration of LTE exposure to AL002 in weeks will also be mapped to one of the following duration categories: < 16 weeks, 16 weeks - < 32 weeks, 32 weeks – < 48 weeks, 48 weeks – < 56 weeks, and ≥ 56 weeks, where 1 week = 7 days.

For the Integrated Analysis, duration of exposure to AL002 and the total number of AL002 doses received will summarize the study drug administration of AL002 collected across the Core Study and the LTE Study. And duration of exposure to AL002 in weeks will also be mapped to one of the following duration categories: < 16 weeks, 16 weeks - < 32 weeks, 32 weeks – < 48 weeks, 48 weeks – < 64 weeks, 64 weeks - < 80 weeks, 80 weeks - < 96 weeks, 96 weeks - < 112 weeks, 112 weeks - < 128 weeks, 128 weeks - < 144 weeks, 144 weeks - < 152 weeks, and ≥ 152 weeks.

Treatment compliance will be summarized as a continuous measure and will also be categorized as < 80%, 80% – 120%, > 120%.

Duration of exposure to AL002, the total number of AL002 doses received, and treatment compliance will be listed.

7.4.3 Adverse Events

AE related terms such as TEAE, SAE, and AESI are defined in Section 6.2.2.

An overall summary of AEs will present the number and percentage of participants who experienced at least 1 TEAE for the following events:

- TEAE (total and by maximum severity),
- Treatment-related TEAE (total and by maximum severity),
- TEAE leading to early study drug discontinuation,
- TEAE leading to study drug interruption,
- Treatment-emergent SAE,
- Treatment-related treatment-emergent SAE,
- Treatment-emergent AESI,
- Treatment-related treatment-emergent AESI,
- TEAE leading to death (i.e., outcome is fatal),

The number and percentage of participants who experienced at least 1 TEAE and the number and percentage of participants who experienced at least 1 treatment-related TEAE will be summarized by SOC, PT, and Severity. For other AEs described below, summaries will be provided by SOC and PT:

- TEAE (total and by severity),
- Treatment-related TEAE (total and by severity),
- TEAE leading to early study drug discontinuation,
- TEAE leading to study drug interruption,
- Treatment-emergent SAE,
- Treatment-related treatment-emergent SAE,

- Treatment-emergent AESI,
- Treatment-related treatment-emergent AESI,
- TEAE leading to death (i.e., outcome is fatal).

AEs will be summarized and listed first in alphabetic order of SOC and then by PT in descending order of total frequency within each SOC.

In addition to the above summary tables, TEAE, treatment-related TEAE, and treatment-emergent SAE will be summarized by PT only, in descending order of total frequency.

In addition to the by-participant data listing of all AEs, separate by-participant data listings will also be provided for the following:

- TEAE leading to early study drug discontinuation,
- Treatment-emergent SAE,
- Treatment-emergent AESI,
- TEAE leading to death.

For Integrated Analysis, all of the above summaries will be presented overall and also by the time intervals of event occurrence defined in Section 7.4.1.2.1. Denominators for percentages of events are determined by the numbers of participants at risk in each interval for each treatment group, which are those participants where [min (last participation day, last dose date + 90 days) – first dose date + 1]/7 is at least equal to the lower bound of the time interval.

For LTE Analysis, the following selected summaries will be provided for events during the LTE Study.

- Overall summary of AEs
- TEAEs by SOC and Preferred Term
- TEAE leading to study drug interruption,
- SAEs
- TEAE leading to death

7.4.3.1 Adverse Events Counting Rules

For Group T-T, at the participant level, the following AE counting rules apply across two studies:

- A participant with more than one different AE in a particular SOC will be counted only once in the total of participants experiencing AEs in that particular SOC.
- A participant having experienced the same event, AE PT, more than once during the study will be counted only once in the number of participants with that event.
- If an event changes in intensity or in seriousness during the study, the participant will be counted only once with the worst grade and seriousness respectively.
- If the causal relationship to the study drug is assessed differently, it will be counted only once by considering the “worst” documented degree of relationship.

For Group P-TC, the same counting rules apply but per study/treatment, i.e., separately counted in Core Study (for placebo) and in LTE Study (for Titration Cohort).

AEs reported with a relationship to study drug of related will be counted as treatment related. If the relationship is missing on the electronic CRF, this event will be included as 'related', and this will be noted.

7.4.3.2 Deaths

If applicable, deaths will be summarized by SOC and PT, and will be listed including any appropriate information where available. All deaths observed in the study will be included in the summary and by-participant data listing.

7.4.4 Columbia Suicide Severity Rating Scale (C-SSRS)

For the C-SSRS, the number and percentage of participants with suicidal ideation, suicidal behavior, and non-suicidal self-injurious behavior as recorded on the C-SSRS scale, will be presented for each visit (refer to Table 7-1 and Table 7-2 for analysis visit window definitions), and overall during the treatment period.

When summarizing the lifetime history of suicidal ideation, suicidal behavior, suicidal ideation or suicidal behavior, and non-suicidal self-injurious behavior, all related data recorded on the Screening/Baseline version will be included regardless of whether the assessment date is prior to, on, or after Core Study Day 1.

When summarizing the baseline (past 6 months for suicidal ideation, or past 2 years for suicidal behavior and non-suicidal self-injurious behavior), only related data recorded on the Screening/Baseline version prior to or on Core Study Day 1 will be included.
Only data recorded on the Since Last Visit version after Core Study Day 1 will be included in the treatment period.

A shift table from Core baseline (past 6 months for suicidal ideation, or past 2 years for suicidal behavior) to each post-baseline visit and to overall during the treatment period will be provided for suicidal ideation, suicidal behavior, and no suicidal ideation or suicidal behavior. For overall, the response with the most severe suicidal ideation and suicidal behavior will be selected for a participant.

All C-SSRS data will be listed.

7.4.5 Laboratory Data

Laboratory data in summary tables and by-participant data listings will be presented in the International System of Units (SI units; Système International d'Unités).

When values are below or above a limit of quantitation, they will be listed as such, and the closest imputed value will be used for calculating summary statistics as specified in Section 7.1.4.

7.4.5.1 Numeric and Categorical Laboratory Results

For laboratory parameters that are continuous in nature, their laboratory data will be presented descriptively for each visit (refer to a Target Day and Core Study Day are based on Core Study Day 1.

[b] LTE Day 1 represents Core Study Day of date of LTE Study Day 1. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit.

Table 7-2. Analysis Visit Windows for C-SSRS Assessments Based on LTE Study Day [a]

Analysis Visit	Target Day	Analysis Visit Window
LTE Baseline	1	≤ 1
LTE Week 4	29	[2, 43]
LTE Week 8	57	[43, 71]
LTE Week 12	85	[72, 99]
LTE Week 16	113	[100, 127]
LTE Week 20	141	[128, 155]
LTE Week 24	169	[156, 183]
LTE Week 28	197	[184, 211]
LTE Week 32	225	[212, 239]
LTE Week 36	253	[240, 267]
LTE Week 40	281	[268, 295]
LTE Week 44	309	[296, 323]
LTE Week 48	337	[324, 365]
LTE Week 56	393	> 365

[a] Target Day and LTE Study Day are based on LTE Study Day 1, unless indicated otherwise.

Table 7-3 and a Target Day and Core Study Day are based on Core Study Day 1.

[b] LTE Day 1 represents Core Study Day of date of LTE Study Date 1. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit.

Table 7-4. Analysis Visit Windows for Hematology, Chemistry and Urinalysis Assessments Based on LTE Study Day [a]

Analysis Visit		Target Day	Analysis Visit Window
LTE Baseline		1	≤ 1
LTE Week 12 (Hematology and Chemistry only)		85	[2, 141]
LTE Week 28	Hematology and Chemistry	197	[142, 239]
	Urinalysis		[2, 337]
LTE Week 40 (Hematology and Chemistry only)		281	[240, 337]
LTE Week 56		393	> 337

[a] Target Day and LTE Study Day are based on LTE Study Day 1.

Table 7-5 for analysis visit window definitions); the actual values and CFB will be summarized. Both baselines will be used (Core baseline and LTE baseline).

Local laboratory data will not be summarized or listed.

All central laboratory data along with the normal ranges when applicable will be listed.

7.4.5.2 Toxicity Grades for Laboratory Results

Participants with a toxicity grade ≥ 3 will be marked in the by-participant data listing.

7.4.6 Electrocardiogram (ECG)

Actual results and CFB values for single 12-lead ECGs (i.e., heart rate (beats/min), RR Interval (msec), QRS Duration (msec), QTcF Interval (msec)) will be summarized descriptively for each visit (refer to Table 7-7 and Table 7-8 for analysis visit window definitions) and separated by predose and post-infusion (refer to Section 7.1.4.2 for handling of predose, post-infusion and "Not Applicable") per each visit. In addition, shift tables from baseline to post-baseline in the Investigator's overall interpretation of the ECG as indicated on the ECG electronic CRF will be provided for each visit. The summary will be separated by measurement time point (predose, post-infusion and "Not Applicable") per visit. Selection of data in the event of multiple records in an analysis visit window is specified in Section 7.1.3.2, separately for measurement time point (predose, post-infusion and "Not Applicable").

For the QTcF parameter as collected on the ECG electronic CRF, the number and percentage of participants in each criterion below will be summarized separated by measurement time point (predose and post-infusion) per visit and overall during the treatment period. For overall, the record with the most severe finding will be selected for a participant.

Of the absolute QTcF interval prolongation:

- > 450 msec,
- > 480 msec,
- > 500 msec.

- Of the CFBs in QTcF interval:
  - > 30 msec,
  - > 60 msec.

The number and percentage of participants in each criterion below (Table 7-37) will be summarized separated by measurement time point (predose and post-infusion) per visit and overall during the treatment period. For overall, the record with the most severe finding will be selected for a participant.

Table 7-37 ECG Parameter Criteria

ECG Parameter	Low Criteria	High Criteria
Heart Rate	< 50 beats/min	> 100 beats/min
RR Interval	< 600 msec	≥ 1200 msec
QRS Duration	< 60 msec	≥ 120 msec

All ECG data as collected on the ECG electronic CRF will be listed.

7.4.7 Vital Signs

Vital signs data will be presented descriptively for each visit (refer to [a] Target Day and Core Study Day are based on Core Study Day 1.
[b] LTE Day 1 represents Core Study Day of first dose date of LTE Study. If no such date, use Core study day of the last visit date among Core visits and LTE screening visit.

Table 7-10 and Table 7-11 for analysis visit window definition) and separated by predose and post-infusion (refer to Section 7.1.4.2 for handling of predose and post-infusion) per each visit; the actual values and CFB will be summarized. Selection of data in the event of multiple records in an analysis visit window is specified in Section 7.1.3.2, separately for measurement time point (predose, post-infusion, and not applicable).

A post-baseline vital signs value is considered treatment-emergent potentially clinically significant (PCS) if it meets both the observed value and the CFB criteria as listed in Table 7-38 during the treatment period. The number and percentage of participants with post-baseline treatment-emergent PCS vital signs will be summarized for each post-baseline visit and overall during the treatment period. The summary will be separated by measurement time point (predose, post-infusion, and not applicable) per visit or overall. For overall, the record with the most severe finding will be selected for a participant, separated by measurement time point (predose, post-infusion, and not applicable). Vital signs with measurement time point missing will only be included in the by-participant data listing.

All vital signs will be listed.

Table 7-38. Criteria for PCS Vital Signs

Parameter	Flag	Criteria[a]	
		Observed Value	CFB
Supine systolic blood pressure (mmHg)	High	≥ 180	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Supine diastolic blood pressure (mmHg)	High	≥ 105	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Supine pulse rate (beats/min)	High	≥ 120	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Weight (kg)	High	—	Increase of ≥ 7%
	Low	—	Decrease of ≥ 7%

a. A post-baseline value is considered potentially clinically significant if it meets both the observed value and the CFB criteria.

7.4.8 Magnetic Resonance Imaging (MRI) for ARIA-E and ARIA-H Events

Incidence of the occurrence of ARIA-E within each post-baseline visit will be summarized by radiographic severity for each visit (refer to Table 7-12 and Table 7-13 for analysis visit window definitions) and overall. The same incidence table will be summarized for ARIA-H. In addition to radiographic severity for ARIA-H, individual radiographic severity for microhemorrhages, leptomeningeal hemosiderosis, and macrohemorrhages for the occurrence of ARIA-H will also be summarized by visit and overall.

In the case of multiple values in the baseline analysis visit window, the rules described in the Section 7.1.3.2 still apply. In the case of multiple values in a post-baseline analysis visit window, the rules described in the Section 7.1.3.2 do not apply to this summary, but the worst-case scenario will be applied as below:

- A participant having a record indicating no ARIA-E and a different record indicating ARIA-E is considered experienced ARIA-E per visit or overall.
- A participant having experienced ARIA-E more than once per visit or overall is counted once in the number of participants with ARIA-E per visit or overall.
- The maximum severity is selected if ARIA-E was observed more than once for a participant per visit or overall post-baseline.

The same rules described above also apply to ARIA-H. In addition, the maximum severity of ARIA-H is selected for a participant per visit or overall post-baseline, and the individual radiographic severity corresponding to the selected ARIA-H will be summarized per visit or overall post-baseline.

APOE genotype, time to the first occurrence, resolution, time to resolution, and reoccurrence will be summarized for participants with ARIA-E. APOE genotype and time to the first occurrence will be summarized for participants with post-baseline ARIA-H.

The number and percentage of participants who had post-baseline ARIA-E but did not have ARIA-H any time post-baseline will be summarized. The number and percentage of participants who had ARIA-H but did not have ARIA-E any time post-baseline will be summarized. Similarly, the number and percentage of participants who had ARIA-H and ARIA-E any time post-baseline will be summarized.

Overall incidence of the occurrence of ARIA-E and ARIA-H will also be summarized by APOE genotype.

All of the MRI summaries described above will also be provided separately for participants with the following APOE genotype(s) (1) e4 carriers (including e2/e4, e3/e4 and e4/e4), and (2) non-e4 carriers (excluding e2/e4, e3/e4 and e4/e4).

For Integrated Analysis, all summaries described in this section will be provided for events across two studies as defined in Section 7.4.1.2. For LTE Analysis, only the overall summary of ARIA will be provided for events during the LTE Study.

For Integrated Analysis, the difference in proportion of participants with ARIA-E events between a slower titration rate over 48 weeks and a faster titration rate over 48 weeks will be estimated by the Cochran-Mantel-Haenszel (CMH) method adjusting for the APOE e4 status. The faster titration rate will be represented by data from the AL002 60 mg/kg treatment group during the first 48 weeks of the Core Study among participants who were on dose titration (i.e., received the first dose on or after July 22, 2021 in the Core Study) and had at least one evaluable post-baseline MRI scan. The slower titration rate will be represented by data from the first 48 weeks of the LTE Study, among Titration Cohort participants who had at least one evaluable post-baseline MRI scan in the LTE Study. Both 90% and 95% CIs for the difference in the ARIA-E events and p-value will be reported from the CMH method. The same analysis will be repeated for ARIA-H.

The statistical tests (the CMH method) of ARIA events between the slower and faster titration groups will not be performed at the first IA at the time of unblinding of the Core Study due to limited data from the LTE study at this IA, but will be performed in all analyses after the first IA.

In the Integrated Analysis, the Kaplan-Meier curves for the time to the first occurrence of ARIA-E during both the Core and LTE Studies will be plotted. For participants who experienced at least one ARIA-E, the time to the first occurrence of ARIA-E is the time from the first dose date to the onset date of the first ARIA-E occurrence. For participants who did not experience ARIA-E, the censor date will be the earlier date of the last MRI scan date, any death date, and the last dose date plus 90 days. Similarly, the Kaplan-Meier curves for the time to the first occurrence of ARIA-H will be plotted.

All MRI findings will be listed.

7.4.9 Ophthalmological Examinations

Incidence of any post-baseline treatment-emergent PCS ophthalmological examinations findings as indicated on the Optical Coherence Tomography, Visual Acuity, Slit Lamp Exam, and Fundoscopy electronic CRFs will be summarized for each visit (refer to Table 7-14 and Table 7-15 for analysis visit window definitions), and overall during the treatment period. For overall, the record with the most severe finding will be selected for a participant. PCS ophthalmological examinations findings are defined as

- On the Optical Coherence Tomography electronic CRF

- Percent CFB in left eye retinal central subfield thickness (in micrometers) ≥ 20%,
- Percent CFB in right eye retinal central subfield thickness (in micrometers) ≥ 20%,
- Percent CFB in left eye subfoveal choroidal thickness (in micrometers) ≥ 20%,
- Percent CFB in right eye subfoveal choroidal thickness (in micrometers) ≥ 20%.

- On the Visual Acuity electronic CRF
  - Left eye best-corrected visual acuity worsen 3 categories since baseline (the higher the best-corrected visual acuity, the worse):
    - 20/32 and 20/30 are pooled and are considered one category,
    - When counting, 3 categories do not include the baseline assessment but include the post-baseline assessment, e.g., from 20/20 at baseline to 20/40 at a post-baseline, it is counted as worsen 3 categories.
  - Right eye best-corrected visual acuity worsen 3 categories since baseline.
- On the Slit Lamp Exam electronic CRF
  - Left Anterior Cell Score by SUN Criteria ≥ 0.5 (the higher the Anterior Cell Score, the worse),
  - Right Anterior Cell Score by SUN Criteria ≥ 0.5.
- On the Fundoscopy electronic CRF
  - Left eye results shown as abnormal (clinically significant),
  - Right eye results shown as abnormal (clinically significant),
  - Left eye results shown as abnormal (not clinically significant),
  - Right eye results shown as abnormal (not clinically significant).

All ophthalmological examinations findings will be listed separately by electronic CRF.

7.4.10 Neurological Examinations

Incidence of any post-baseline treatment-emergent PCS neurological examinations findings as indicated on the Neurological Exam electronic CRF will be summarized for each visit (refer to Table 7-16 and Table 7-17 for analysis visit window definitions) and overall during treatment periods. For overall, the record with the most severe finding will be selected for a participant. Shift tables from baseline to post-baseline will be provided.

All neurological examinations findings will be listed.

7.4.11 Physical Examinations (PE)

All PE findings will be listed.

7.4.12 Other Safety Assessments

7.4.12.1 Pregnancy Test

Reproductive status and pregnancy test results at any visit will be listed.

7.5 Pharmacokinetic Endpoints

All PK summaries will be performed as the integrated analysis based on the PKS according to the actual treatment received. The PKS will include all participants in the ATS that received AL002, had at least one

post-dose measurable concentration, and are non-e4/e4. The treatment groups will include AL002 15 mg/kg, AL002 40 mg/kg, AL002 60 mg/kg, AL002 40+60 mg/kg, and LTE titration. There are two titration strategies specified in the protocol (Section 5.1). If there are sufficient number of participants who follow the titration algorithm 2, the PK summary analysis will display both LTE titration Algorithm 1 and Algorithm 2 groups instead of LTE titration groups.

AL002 concentration will be summarized by analysis visit (refer to Table 7-22 to Table 7-25 for analysis visit window definitions) and nominal time point as collected, separately for serum and CSF PK data. Summary statistics will include coefficient of variation (CV) as percent and geometric mean in addition to the descriptive statistics (excluding Q1 and Q3) described in Section 7.1.

AL002 mean (+ SD) concentration-time data will be plotted (linear and semi-log) by elapsed time since the first study drug administration (in weeks, i.e., (time of collection – time of the first study drug administration)/(24×7)) and treatment group, separately for serum and CSF PK. The same plot (linear and semi-log) will be repeated for the first 28 days on treatment period, but by days (i.e., (time of collection – time of the first study drug administration)/24) instead of weeks.

For the summaries and mean plots of AL002 concentrations, concentrations that are below LLOQ (below the limit of quantifications (BLQs)) before the first measurable concentrations on Study Day 1 will be set to zero, and all BLQs after Study Day 1 will be set to missing. The rules specified in Section 7.1.4.1.1 do not apply to PK.

Potential correlations of serum and/or CSF PK data with demographics, safety (including QT changes), efficacy, and PD measures may be explored, as data allow. Additional modeling, including population PK analysis and/or PK/PD analysis to characterize these correlations may be performed. These additional analyses of PK/PD data will be covered in a separate analysis plan and reported separately from the CSR.

The AL002 concentration data will be listed for the ATS..

7.6 Efficacy Analyses

All efficacy endpoints will be summarized with the Integrated Analysis for the FAS. Analysis sets are defined in Section **Error! Reference source not found.**.

The main estimand as described in Section 0 will be used for all efficacy analyses. The supportive estimand may be used as additional analysis for some efficacy endpoints.

Analysis visit windows for efficacy data are defined in Section 7.1.1.2.2. Baseline is defined in Section 7.1.2.

7.6.1 Descriptive Summaries of Efficacy Endpoints

The integrated descriptive summary of an efficacy endpoint including the Placebo Data will summarize all the data collected in the Core Study and in the LTE Study with descriptive statistics, by individual placebo/TC, AL002 15 mg/kg, 40 mg/kg, and 60 mg/kg, and the TC treatment groups, and AL002 40 and 60 mg/kg combined group.

The CFB and PCFB will be based on the Core baseline for placebo/TC, AL002 15 mg/kg, 40 mg/kg, and 60 mg/kg, and AL002 40 and 60 mg/kg combined treatment groups. The CFB and PCFB for the TC will be based on the LTE baseline. And all analysis visits from the Core and LTE Studies will be included.

Longitudinal trend (line-plot) figures (group mean [unadjusted] of change from Core baseline ± SEM (standard error of the mean) over time at each analysis visit) over the Core + LTE periods for placebo/TC, AL002 15 mg/kg, 40 mg/kg, and 60 mg/kg treatment groups will be created.

7.6.2 Analyses of Efficacy Endpoints

For Integrated Analysis, the analyses as described in the Core Study SAP will be repeated based on the integrated data up to Week 96 since the initiation of study treatment from both the Core Study and the LTE study for the AL002 treatment groups and the data from the Core Study and the screening visit of LTE study for the placebo treatment group. This includes the fitting of MMRM and pMMRM models, to obtain estimates of least square mean difference in CFB and percent slowing of decline (from MMRM) and proportional treatment effect (from pMMRM).

A pMMRM approach (G. Wang et al., 2022) will be used as the primary analysis of all efficacy endpoints. Conceptually, the pMMRM is similar to the Cox proportional hazards model, as it models the treatment effect as a single proportional difference at each post-baseline visit. It uses time as a categorical variable like an MMRM and thus avoids the linearity assumption. On the other hand, pMMRM takes on the assumption of a proportional treatment effect of a linear mixed-effect (LME) model and thus uses assessments more efficiently than an MMRM model.

A restricted maximum likelihood based MMRM will be used as a supportive analysis to assess the primary endpoint. The SAS® MIXED procedure will be used to fit an MMRM with CFB in CDR-SB at each scheduled post-baseline visit (Week 24, 48, 72, and 96) as the dependent variables and the fixed effects will include following items:

- Treatment group,
- Visit (categorical, as week),
- Visit-by-treatment interaction,
- Core Baseline CDR-SB score (covariate),
- APOE e4 status (covariate, e4 carrier vs non-e4 carrier).

An unstructured covariance matrix will be used to model within-participant variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence, the following tests will be used in sequence:

- Heterogeneous Toeplitz (TOEPH) covariance structure,
- Heterogeneous first-order autoregressive (ARH(1)) covariance structure,
- Heterogeneous compound symmetry (CSH) covariance structure,
- Toeplitz (TOEP) covariance structure,
- First-order autoregressive (AR(1)) covariance structure,
- Compound symmetry (CS) covariance structure.

In the case that a structured variance-covariance matrix is used to enable the model to converge, the "sandwich" estimator of the variance-covariance matrix will be employed by using the “empirical” option in the SAS PROC MIXED procedure.

The MMRM and pMMRM modeling analyses will not be performed at the first IA at the time of unblinding of the Core Study due to limited data from the LTE study at this IA, but will be performed in all analyses after the first IA.

7.7 Exploratory PD Biomarker Endpoints and Estimands

All biomarker endpoints will be analyzed with the Integrated Analysis for the FAS using the main estimand. The main estimand will be used for all biomarker analyses, unless otherwise specified.

7.7.1 List of Biomarkers

Biomarkers are listed in Table 7-39.

Table 7-39. Biomarkers List

Biomarker Type	Biomarker
CSF	• sTREM2 (target engagement) • IL1RA (TREM2 engagement) • Osteopontin (TREM2 engagement) • pTau217 (amyloid and Tau) • MTBR Tau-243 (amyloid and Tau) • pTau181 (amyloid)* • Aβ42 (amyloid) • Aβ40 (amyloid) • Aβ42/40 (amyloid) • GFAP (neuroinflammation and neurodegeneration) • CSF1R (microglial survival and proliferation) • NfL (neurodegeneration) • YKL-40 (neuroinflammation) • Total Tau (neurodegeneration) • IL-6 (neuroinflammation) • s100b (neuroinflammation) • Neurogranin (synapse loss) • NPTX2 (synapse degeneration) • SNAP25 (synapse degeneration)
Plasma	• IL1RA (TREM2 engagement) • pTau217 (amyloid and Tau) • MTBR Tau-243 (amyloid and Tau)* • pTau181 (amyloid)* • Aβ42 • Aβ40 • Aβ42/40 • GFAP (neuroinflammation and neurodegeneration) • NfL (neurodegeneration)

Biomarker Type	Biomarker
Amyloid PET (normalized to whole cerebellum)	• Composite ROIs: ○ Global cortical average, SUVR measure ○ Global, centiloids measure • Roll-up ROIs, SUVR measure: ○ Frontal ○ Lateral temporal ○ Lateral parietal ○ Cingulate ○ Lateral occipital
Tau PET (normalized to cortical grey matter of cerebellum)	• Roll-up ROIs, SUVR measure: ○ Medial temporal ○ Temporal ○ Frontal ○ Cingulate ○ Parietal ○ Occipital ○ Whole cortical gray cortex ○ Temporoparietal • Rowe metatemporal composite ROI, SUVR measure • Jack metatemporal composite ROI, SUVR measure
MRI	• Volumetric parameters: ○ Whole Brain ○ Hippocampus ○ Ventricles ○ Temporal cortex ○ Parietal cortex

CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; PET = positron emission tomography; ROI = region of interest; SUVR = standardized uptake value ratio.
*if available

7.7.2 Descriptive Summaries of Biomarker Endpoints

The integrated descriptive summary of a biomarker endpoint including the Placebo Data will summarize all the data collected in the Core Study and in the LTE Study with descriptive statistics, by individual placebo/TC, AL002 15 mg/kg, 40 mg/kg, and 60 mg/kg, and the TC treatment groups, and AL002 40 and 60 mg/kg combined group.

The CFB and PCFB will be based on the Core baseline for placebo/TC, AL002 15 mg/kg, 40 mg/kg, and 60 mg/kg, and AL002 40 and 60 mg/kg combined treatment groups. The CFB and PCFB for the TC will be based on the LTE baseline. And all analysis visits from the Core and LTE Studies will be included.

The integrated descriptive summaries for Tau PET parameters will be based on the subset with redefined core baseline (participants with either pre-dose Tau PET in the Core study if available or the first evaluable post-dose Tau PET scan result in the Core study if pre-dose PET scan in the Core study is missing).

Longitudinal trend (line-plot) figures (group mean [unadjusted] of change from Core baseline ± SEM over time at each analysis visit) over the Core + LTE periods for placebo/TC, AL002 15 mg/kg, 40 mg/kg, and 60 mg/kg treatment groups will be created.

7.7.3 Pharmacodynamic (PD) Assessment of Biomarker Endpoints

For Integrated Analysis, similar analyses listed in section 7.6.2 for efficacy endpoints will be provided for biomarker endpoints. Specifically, for CSF and plasma biomarkers, volumetric MRI, amyloid PET and Tau PET parameters [Table 7-39], the analyses will be based on the integrated data up to Week 96 since the initiation of study treatment from both the Core Study and the LTE study for the treatment groups and the data from the Core Study and the LTE screening data for the placebo treatment group. Specifically, the MMRM will be fit with CFB in biomarkers up to Week 96 as the dependent variable, and treatment group, categorical visit, visit-by-treatment interaction, baseline (from the Core Study) biomarker, and APOE e4 status of carrier vs. non-carrier as fixed effects.

Input for the models will be non-missing data at all analysis visits up to and including Week 96, as specified in Tables Table 7-12, Table 7-28, Table 7-30, Table 7-32, and Table 7-36. Treatment comparisons will be reported for specified visits as indicated below:

- Plasma biomarkers:
  - AD-pathology (Aβ42/40, pTau217): week 12, 24, 48, 72 and 96
  - AD-pathology (MTBR Tau-243 [if available]): week 12, 24, 48, 72 and 96
  - AD-pathology (pTau181 [if available]): week 16, 36, 60 and 84
  - Target engagement (IL1RA): week 1, 2, 4, 6, 8, 12, 24, 36, 48, 72 and 96
  - Neurodegeneration (NfL, GfAP): week 12, 24, 48, 72 and 96
- CSF biomarkers: week 6, 48, 72 and 96
- Amyloid PET parameters: week 48 and 96
- Tau PET parameters: week 48, 72 and 96
- Volumetric MRI parameters: week 48, 72 and 96

Model results, including treatment comparisons will also be obtained as “overall” for the average over all analysis visits in the model.

For Tau PET parameters [Table 7-39], a pMMRM model will be additionally conducted. The integrated PD analyses via MMRM and pMMRM will be based on the subset with redefined core baseline.

For amyloid PET centiloids, the number of participants with amyloid clearance (positive [centiloid ≥ 24.1] at core baseline and negative [centiloid < 24.1] post core baseline (separately for week 48 and week 96), and percentage with 95% CI (exact mid-p method), will be summarized based on the integrated data up to Week 96 since the initiation of study treatment from both the Core Study and the LTE study for the treatment groups and the data from the Core Study and the LTE screening data for the placebo treatment group. Treatment comparison (vs. placebo) at week 48 and week 96 will be based on the exact mid-p method.

Additional integrated analyses based on supportive estimand will be provided for Tau PET parameters (descriptive summary, MMRM and pMMRM) [Table 7-39] for the subset with redefined baseline, and amyloid PET parameters (descriptive summary and MMRM) [Table 7-39].

The MMRM and pMMRM modeling analyses will not be performed at the first IA at the time of unblinding of the Core Study due to limited data from the LTE study at this IA, but will be performed in all analyses after the first IA.

7.8 Immunogenicity Endpoints

The exploratory analyses for immunogenicity endpoints will be performed on the Non-e4/e4 Set participants who had at least one post-baseline sample evaluable for immunogenicity.

7.8.1 Antidrug Antibodies (ADAs)

Blood serum samples will be collected for determination of ADAs. In addition to titer numerical results, blood serum results will be classified as Positive, Negative or Unknown (missing, non-evaluable, etc.).

The number and percentage of participants having positive or negative results will be summarized by visit and treatment group. The titer numerical results will be descriptively summarized by visit and treatment group. Shift from baseline in blood serum classes will be summarized by visit (refer to Table 7-20 and Table 7-21 for analysis visit window definitions) and treatment group using the frequency count and percentage of participants in each category.

A listing of ADAs including all participants with available ADA data will be provided.

8. ANALYSES TO BE PERFORMED AT INTERIM

In general, analyses outlined in this SAP apply to the final analysis, when the LTE study concludes.

The scope of the first IA at the time of unblinding of the Core Study is specified in Section 8.1.

The scope of the subsequent IAs will be the same (Section 8.1), except that the inferential statistical analysis (Section 7.6.2) will be performed when there is sufficient data at the data cutoff date of the IA.

8.1 Interim Analyses at the Time of Unblinding of the Core Study

The analyses specified in this section will be performed at the time of unblinding of the Core Study. For each summary, the corresponding by-participant listing will be provided.

8.1.1 Participant Disposition, Demographics and Baseline Characteristics

Participant disposition specified in Section 7.2.1 will be summarized for the ATS.

Demographics and baseline characteristics specified in Section 7.3.1 will be summarized for the ATS-LTE.

8.1.2 Efficacy Analyses

For each efficacy endpoint, the integrated descriptive summary and the longitudinal trend figure specified in Section **Error! Reference source not found.** will be provided for the main estimand in the FAS.

8.1.3 Safety Analyses

The integrated summary of extent of exposure to study drug as specified in Section 7.4.1 will be provided for the Non-e4/e4 Set.

The following integrated summaries of TEAE will be provided overall across two studies and by the time interval of TEAEs occurrence as specified in Section 7.4.1.2.1 for the Non-e4/e4 Set:

- Summary of TEAEs
- Incidence of TEAEs by Preferred Term
- Incidence of TEAEs Leading to Early Study Drug Discontinuation by System Organ Class and Preferred Term
- Incidence of Treatment-Emergent SAE by Preferred Term

For the integrated summaries of TEAE by time interval of TEAEs occurrence, the same TEAE counting rules apply per each time interval.

The integrated summaries of ARIA as specified in Section 7.4.8 will be provided for the Non-e4/e4 Set.

The integrated descriptive summaries of continuous safety endpoints as specified in Section 7.4.1.2 will be provided for the Non-e4/e4 Set for the laboratory data, ECG, and Vital Signs. Integrated summaries of treatment-emergent potentially clinically significant values will be provided for the Non-e4/e4 Set for ECG and Vital Signs.

PK, ADA, C-SSRS, eye exam, neurological exam, or other safety analysis may be performed at interim analyses after the first IA.

8.1.4 Biomarker Analyses

For CSF and plasma biomarkers, volumetric MRI, amyloid PET and Tau PET parameters [Table 7-39], the integrated descriptive summaries [tables] specified in Section 7.7.2**Error! Reference source not found.** will be provided for the main estimand in the FAS.

9. STATISTICAL SOFTWARE

SAS® Version 9.4 or later in the UNIX environment will be used for all statistical analyses.

10. REFERENCES

Belenguez, Celine, Fahri Kukukali, Iris E Jansen, Luca Kleineidam, Sonia Moreno-Grau, Najaf Amin, Adam C Naj, Rafael Campos-Martin, Benjamin Grenier-Boley, Victor Andrade, Peter A Holmans, Anne Boland, Vincent Damotte, Sven J van der Lee, Marcos R Costa, Teemu Kuulasmaa, Qiong Yang, Itziar de Rojas, Joshua C Bis, Amber Yaqub, Ivana Prokic, Julien Chapuis, …, and Jean-Charles Lambert. 2022. "New Insights into the Genetic Etiology of Alzheimer's Disease and Related Dementias." *Nature Genetics* 54, 412-436.

Folstein, Marshal F, Susan E Folstein, and Paul R McHugh. 1975. "'Mini-Mental State': A Practica E Method for Grading the Cognitive State of Patients for the Clinician." *Journal of Psychiatric Research* 12 (3): 189–98..

Galasko, D, D Bennett, M Sano, C Ernesto, R Thomas, M Grundman, and S Ferris. 1997. "An Inventory to Assess Activities of Daily Living for Clinical Trials in Alzheimer's Disease. The Alzheimer's Disease Cooperative Study." *Alzheimer Disease and Associated Disorders* 11 Suppl 2: S33-9.

Godin, Judith, Janice Keefe, and Melissa K Andrew. 2017. "Handling Missing Mini-Mental State Examination (MMSE) Values: Results from a Cross-Sectional Long-Term-Care Study." *Journal of Epidemiology* 27 (4): 163–71. https://doi.org/10.1016/j.je.2016.05.001.

Kennedy, Richard E, Gary R Cutter, Guoqiao Wang, and Lon S Schneider. 2015. "Using Baseline Cognitive Severity for Enriching Alzheimer's Disease Clinical Trials: How Does Mini-Mental State Examination Predict Rate of Change?" *Alzheimer's & Dementia: Translational Research & Clinical Interventions* 1 (1): 46–52.

Kennedy, Richard E, Guoqiao Wang, Gary R Cutter, and Lon S Schneider. 2015. "O1-10-02: How Does Differential Effect of Treatment in ApoE-ε4+ Carriers Change Clinical Trial Design in Alzheimer's Disease?" *Alzheimer's & Dementia* 11 (7S_Part_3): P154–P154.

Little, Roderick J A, and Donald B Rubin. 2019. *Statistical Analysis with Missing Data*. Vol. 793. John Wiley & Sons.

O'Bryant, Sid E, Laura H Lacritz, James Hall, Stephen C Waring, Wenyaw Chan, Zeina G Khodr, Paul J Massman, Valerie Hobson, and C Munro Cullum. 2010. "Validation of the New Interpretive Guidelines for the Clinical Dementia Rating Scale Sum of Boxes Score in the National Alzheimer's Coordinating Center Database." *Archives of Neurology* 67 (6): 746–49.

Randolph, Christopher. 2012. *RBANS Update : Repeatable Battery for the Assessment of Neuropsychological Status*. Bloomington, Minn. : NCS Pearson : PsychCorp.

Wang, Guoqiao, Richard E Kennedy, Gary R Cutter, and Lon S Schneider. 2015. "Effect of Sample Size Re-Estimation in Adaptive Clinical Trials for Alzheimer's Disease and Mild Cognitive Impairment." *Alzheimer's & Dementia: Translational Research & Clinical Interventions* 1 (1): 63–71.

Wang, Guoqiao, Lei Liu, Yan Li, Andrew J Aschenbrenner, Randall J Bateman, Paul Delmar, Lon S

Schneider, Richard E Kennedy, Gary R Cutter, and Chengjie Xiong. 2022. “Proportional Constrained Longitudinal Data Analysis Models for Clinical Trials in Sporadic Alzheimer’s Disease.” *Alzheimer’s & Dementia: Translational Research & Clinical Interventions* 8 (1): e12286.

Wang, Jinping, Veronika Logovinsky, Suzanne B Hendrix, Stephanie H Stanworth, Carlos Perdomo, Lu Xu, Shobha Dhadda, et al. 2016. “ADCOMS: A Composite Clinical Outcome for Prodromal Alzheimer's Disease Trials.” *Journal of Neurology, Neurosurgery &Amp;Amp; Psychiatry* 87 (9): 993 LP – 999. https://doi.org/10.1136/jnnp-2015-312383.

Wessels AM, Andersen SW, Dowsett SA, Siemers ER. The Integrated Alzheimer's Disease Rating Scale (iADRS) Findings from the EXPEDITION3 Trial. J Prev Alzheimers Dis. 2018;5(2):134-136. doi: 10.14283/jpad.2018.10. PMID: 29616706.

Wessels AM, Siemers ER, Yu P, Andersen SW, Holdridge KC, Sims JR, Sundell K, Stern Y, Rentz DM, Dubois B, Jones RW, Cummings J, Aisen PS. A Combined Measure of Cognition and Function for Clinical Trials: The Integrated Alzheimer's Disease Rating Scale (iADRS). J Prev Alzheimers Dis. 2015 Dec 1;2(4):227-241. doi: 10.14283/jpad.2015.82. PMID: 27019841; PMCID: PMC4806404.

Westfall, Peter H, and Alok Krishen. 2001. “Optimally Weighted, Fixed Sequence and Gatekeeper Multiple Testing Procedures.” *Journal of Statistical Planning and Inference* 99 (1): 25–40.

MSB DOCS™

Validation Report

1 ✓

Subject CN	TAIGLE LLC
Subject DN	EMAILADDRESS=operations@msbdocs.com,CN=TAIGLE LLC,OU=MSB,O=TAIGLE LLC,L=Irvine,ST=California,C=US
Email	operations@msbdocs.com
Serial #	944980637215987349094739815700443967 79
Issuer DN	CN=Entrust Class 3 Client CA - SHA256,OU=(c) 2015 Entrust, Inc. - for authorized use only,OU=See www.entrust.net/legal-terms,O=Entrust, Inc.,C=US
Signing Time	25 Oct 2024 18:16:49 (-04:00)

✓ The Certificate chain was successfully built to a Trusted Root Certificate.

✓ The Signer's identity is valid.

✓ The Document has not been modified since the signature was applied.

This page was added to the original document by the MSB Validation Service (SVS) as part of the process to convert active signature block content into inactive text. A full validation report of each signature is generated and cross-referenced using a numeric footnote annotation.

DocUUID : 7f778de0-046e-479d-bb51-d30ce4769ceb

MSB DOCS™

Audit Trail Report

Time Stamp	User	Document	Action	Details
25 Oct 2024 12:22:46 (-04:00)	Emily Moray UUID : 1f8a25cb-96f0-48db-962e-77742002754e Email : emily.moray@ecrscorp.com IP Address : 216.180.71.241 OS: Windows, Browser: Chrome, Device: Desktop		Started	The custodian composed the ePak succesfully. Subject: AL002-LTE SAP_V1.0_20241025 ePak UUID: 7d72eb86-23bf-4560-9e8a-ec5b17cdd9cf
25 Oct 2024 12:22:46 (-04:00)	Dean Rutty UUID : cf05f229-4a1f-4d58-ac25-8bd2e3adbcce Email : dean.rutty@ecrscorp.com		Request Sent	Sign request sent to ePak recipient.
25 Oct 2024 12:22:47 (-04:00)	Francis Tang UUID : 7ceff508-b0bf-428b-8092-b96c1846754e Email : francis.tang@ecrscorp.com		Request Sent	Sign request sent to ePak recipient.
25 Oct 2024 12:22:47 (-04:00)	Arthur Mayorga UUID : c0c8c8d4-27fe-4689-8eed-59417ccb7f59 Email : arthur.mayorga@alector.com		Request Sent	Sign request sent to ePak recipient.
25 Oct 2024 12:22:48 (-04:00)	Yong Tang UUID : 1fbe6cc4-d47b-407e-ab54-d89b6464a7a2 Email : yong.tang@alector.com		Request Sent	Sign request sent to ePak recipient.
25 Oct 2024 12:24:40 (-04:00)	Francis Tang UUID : 7ceff508-b0bf-428b-8092-b96c1846754e Email : francis.tang@ecrscorp.com IP Address : 209.141.143.2 OS: Windows, Browser: Edge, Device: Desktop	Name : AL002-LTE SAP_V1.0_20241025.pdf UUID : 7f778de0-046e-479d-bb51-d30ce4769ceb Document Source : Application	Document Viewed	Document viewed by signer.
25 Oct 2024 12:25:09 (-04:00)	Francis Tang UUID : 7ceff508-b0bf-428b-8092-b96c1846754e Email : francis.tang@ecrscorp.com IP Address : 209.141.143.2 OS: Windows, Browser: Edge, Device: Desktop	Name : AL002-LTE SAP_V1.0_20241025.pdf UUID : 7f778de0-046e-479d-bb51-d30ce4769ceb Document Source : Application	Signed	The recipient signed the document after authentication via login password. Signing Policy: Signature (21CFR) Comments: None Reason: I approve this document. Consent: I understand that my Electronic Signature is Equivalent to my Handwritten Signature and is therefore legally binding. My Electronic Signature will remain unique to me, and under no circumstance I am allowed to disclose my password to any individual which may allow unauthorized access to system. I understand that I am accountable and responsible for all actions associated with my Electronic Signature.
25 Oct 2024 12:42:40 (-04:00)	Yong Tang UUID : 1fbe6cc4-d47b-407e-ab54-d89b6464a7a2 Email : yong.tang@alector.com IP Address : 108.7.221.106 OS: Windows, Browser: Edge, Device: Desktop	Name : AL002-LTE SAP_V1.0_20241025.pdf UUID : 7f778de0-046e-479d-bb51-d30ce4769ceb Document Source : Application	Document Viewed	Document viewed by signer.

MSB DOCS™

Audit Trail Report

Time Stamp	User	Document	Action	Details
25 Oct 2024 12:43:43 (-04:00)	Yong Tang UUID : 1fbe6cc4-d47b-407e-ab54-d89b6464a7a2 Email : yong.tang@alector.com IP Address : 108.7.221.106 OS: Windows, Browser: Edge, Device: Desktop	Name : AL002-LTE SAP_V1.0_20241025.pdf UUID : 7f778de0-046e-479d-bb51-d30ce4769ceb Document Source : Application	Signed	The recipient signed the document after authentication via login password. Signing Policy: Signature (21CFR) Comments: None Reason: I approve this document. Consent: I understand that my Electronic Signature is Equivalent to my Handwritten Signature and is therefore legally binding. My Electronic Signature will remain unique to me, and under no circumstance I am allowed to disclose my password to any individual which may allow unauthorized access to system. I understand that I am accountable and responsible for all actions associated with my Electronic Signature.
25 Oct 2024 15:39:00 (-04:00)	Dean Rutty UUID : cf05f229-4a1f-4d58-ac25-8bd2e3adbcce Email : dean.rutty@ecrscorp.com IP Address : 99.249.130.9 OS: iOS, Browser: Mobile Safari, Device: mobile	Name : AL002-LTE SAP_V1.0_20241025.pdf UUID : 7f778de0-046e-479d-bb51-d30ce4769ceb Document Source : Application	Document Viewed	Document viewed by signer.
25 Oct 2024 15:40:05 (-04:00)	Dean Rutty UUID : cf05f229-4a1f-4d58-ac25-8bd2e3adbcce Email : dean.rutty@ecrscorp.com IP Address : 99.249.130.9 OS: iOS, Browser: Mobile Safari, Device: mobile	Name : AL002-LTE SAP_V1.0_20241025.pdf UUID : 7f778de0-046e-479d-bb51-d30ce4769ceb Document Source : Application	Signed	The recipient signed the document after authentication via login password. Signing Policy: Signature (21CFR) Comments: Dean Rutty on behalf of Michael Edwardes. Reason: I approve this document. Consent: I understand that my Electronic Signature is Equivalent to my Handwritten Signature and is therefore legally binding. My Electronic Signature will remain unique to me, and under no circumstance I am allowed to disclose my password to any individual which may allow unauthorized access to system. I understand that I am accountable and responsible for all actions associated with my Electronic Signature.
25 Oct 2024 15:40:05 (-04:00)	Dean Rutty UUID : cf05f229-4a1f-4d58-ac25-8bd2e3adbcce Email : dean.rutty@ecrscorp.com IP Address : 99.249.130.9 OS: iOS, Browser: Mobile Safari, Device: mobile	Name : AL002-LTE SAP_V1.0_20241025.pdf UUID : 7f778de0-046e-479d-bb51-d30ce4769ceb Document Source : Application	Starred By Sign Comment	ePak starred by a sign comment.
25 Oct 2024 17:56:54 (-04:00)	Arthur Mayorga UUID : c0c8c8d4-27fe-4689-8eed-59417ccb7f59 Email : arthur.mayorga@alector.com IP Address : 96.227.107.27 OS: Mac OS, Browser: Chrome, Device: Desktop	Name : AL002-LTE SAP_V1.0_20241025.pdf UUID : 7f778de0-046e-479d-bb51-d30ce4769ceb Document Source : Application	Document Viewed	Document viewed by signer.

MSB DOCS™

Audit Trail Report

Time Stamp	User	Document	Action	Details
25 Oct 2024 18:16:48 (-04:00)	Arthur Mayorga UUID : c0c8c8d4-27fe-4689-8eed-59417ccb7f59 Email : arthur.mayorga@alector.com IP Address : 96.227.107.27 OS: Mac OS, Browser: Chrome, Device: Desktop	Name : AL002-LTE SAP_V1.0_20241025.pdf UUID : 7f778de0-046e-479d-bb51-d30ce4769ceb Document Source : Application	Signed	The recipient signed the document after authentication via login password. Signing Policy: Signature (21CFR) Comments: None Reason: I approve this document. Consent: I understand that my Electronic Signature is Equivalent to my Handwritten Signature and is therefore legally binding. My Electronic Signature will remain unique to me, and under no circumstance I am allowed to disclose my password to any individual which may allow unauthorized access to system. I understand that I am accountable and responsible for all actions associated with my Electronic Signature.
25 Oct 2024 18:16:48 (-04:00)	Emily Moray UUID : 1f8a25cb-96f0-48db-962e-77742002754e Email : emily.moray@ecrscorp.com		Completed	The ePak is completed successfully.