STATISTICAL ANALYSIS PLAN

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Investigational Drug:	AL002
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Protocol Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of AL002 in Participants with Early Alzheimer's Disease

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
[^{18}F]MK-6240	fluorine-18 MK-6240
AD	Alzheimer's disease
ADA	antidrug antibodies
ADCS-iADL	AD cooperative study - instrumental activities of daily living
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
AIC	Akaike information criterion
anti-HBcAb	total hepatitis B core antibody
APOE	apolipoprotein E
APOE e4	apolipoprotein E epsilon 4
APS	amyloid probability score
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
BIC	Bayesian information criterion
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
CNS	central nervous system
COA	clinical outcome assessment

Abbreviation	Term
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
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
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
iADRS	integrated Alzheimer's disease rating scale
HIV	human immunodeficiency virus
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
LME	linear mixed-effect
LP	lumbar puncture
LSM	least squares means
LTE	long-term extension
MAR	missing at random
Max	maximum
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration

Abbreviation	Term
MCMC	Markov chain Monte-Carlo
MCI	mild cognitive impairment
MCV	mean corpuscular volume
MDRD	modification of diet in renal disease
MedDRA	medical dictionary for regulatory activities
MI	multiple imputation
Min	minimum
ML	maximum likelihood
mmHg	millimeter of mercury
MMRM	mixed-effects model for repeated measures
MMSE	mini-mental status examination
MNAR	missing not at random
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
PLS	partial least squares
PMM	pattern mixture model
pMMRM	proportional MMRM
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

Abbreviation	Term
ROI	region of interest
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	Statistical Analysis Software, SAS Institute
SD	standard deviation
SE	standard error
SFU	safety follow-up
SI	international system
SOC	system organ class
SOP	standard operating procedure
SS	safety set
SUVR	standardized uptake value ratio
tTau	total tau
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
UN	unstructured
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) outlines the statistical methods for the display, summary and analysis of data collected within the scope of Alector Inc. Protocol AL002-2, Version 7.0, dated 20 June 2023. The purpose of this plan is to provide general guidelines from which the analysis will proceed. Deviations from these guidelines must be substantiated by a sound statistical rationale and will be documented in the clinical study report (CSR). If there are differences between the protocol and the SAP, this SAP will take precedence.

The SAP should be read in conjunction with the study protocol and the case report forms (CRFs). This version of the SAP has been developed using version 7.0 of the protocol mentioned above and version 10.0 of the annotated CRF dated 21 March 2024.

2. STUDY OBJECTIVES AND ENDPOINTS

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

Table 2-1. Study Objectives, Endpoints and Estimands

Primary Objective	Primary Efficacy Endpoint and Primary Estimand

To evaluate the efficacy of AL002 in participants with early Alzheimer's disease (AD) in delaying disease progression compared to placebo.	*Primary Efficacy Endpoint:*
	Disease progression as measured by the change from baseline (CFB) in Clinical Dementia Rating – Sum of Boxes (CDR-SB) score to Weeks 24, 48, 72, 96.
	Primary Estimand for Primary Efficacy Endpoint:
	The primary clinical question of interest is the potential relative treatment difference between AL002 and placebo, across all post-baseline timepoints in adult participants with early AD while on study medication, regardless of other interventions.
	The estimand is described by the following attributes:
	• Treatment condition: while on study treatment regardless of other interventions.
	• Target population: adult participants with early AD excluding apolipoprotein E (APOE) epsilon 4 (e4)-homozygous (e4/e4) participants as defined by the protocol inclusion/exclusion criteria.
	• Primary endpoint: CFB in CDR-SB score to Weeks 24, 48, 72, and 96.
	• 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,
	  ○ 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.

Secondary Objectives	**Secondary Efficacy Endpoints and Estimand**
To evaluate the efficacy of AL002 in participants with early AD as measured by the rate of change in clinical outcome assessments (COAs).	*Secondary Efficacy Endpoints:* • CFB in Mini Mental State Examination (MMSE) score to Week 24, 48, 72, and 96.

	• CFB in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score to Week 24, 48, 72, and 96. • CFB in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog13) score to Week 24, 48, 72, and 96. • CFB in Alzheimer's Disease Cooperative Study - Activities of Daily Living - Mild Cognitive Impairment (ADCS-ADL-MCI) score to Week 24, 48, 72, and 96. • CFB in Alzheimer's Disease Composite Score (ADCOMS) to Week 24, 48, 72, and 96. • CFB in modified integrated Alzheimer's Disease Rating Scale (iADRS) to Week 24, 48, 72, and 96. *Main Estimand for Secondary Efficacy Endpoints:* The main estimand for the secondary efficacy endpoints is defined with similar attributes as for the primary estimand except that it is endpoint specific.
Safety Objectives	**Safety Endpoints**
To evaluate the safety and tolerability of AL002 in participants with early AD.	• Incidences of adverse events (AEs), including AEs of special interest (AESIs) and serious AEs (SAEs). • CFBs in vital signs, physical findings, neurological findings, ophthalmological findings, electrocardiogram (ECG) findings, and clinical laboratory results. • Magnetic resonance imaging (MRI) abnormalities. • Columbia-suicide severity rating scale (C-SSRS).
Pharmacokinetic (PK)	**PK Endpoints**
To estimate the concentration of AL002 in participants with early AD in serum and cerebrospinal fluid (CSF), when available.	• Serum PK concentrations of AL002. • CSF PK concentrations of AL002 (when available).
Exploratory Objectives	**Exploratory Pharmacodynamic (PD) Biomarker Endpoints**
To evaluate the effects of AL002 in participants with early AD on exploratory PD biomarkers	• CFBs in levels of soluble triggering receptor expressed on myeloid cells 2 (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 colony-stimulating factor-1 receptor (CSF1R), interleukin 1 receptor antagonist (IL1RN), osteopontin, chitinase-3-like protein 1 (YKL-40)).

	• CFBs in levels of biomarkers related to AD pathology in CSF and/or plasma (including but not limited to amyloid beta (1-40) (Aβ40), amyloid beta (1-42) (Aβ42), phosphorylated tau (pTau), total tau (tTau)). • CFBs in levels of neurodegeneration biomarkers in plasma and CSF (e.g., neurofilament light chain (NfL)). • CFBs in brain volume, assessed by volumetric MRI. • CFBs in brain pathological tau burden as assessed by Tau-specific positron emission tomography (PET, 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). • CFBs for in-clinic speech measurements via the Winterlight Labs speech assessment (WLSA, for participants who agree to participate in the optional assessment only). *Main Estimand for Exploratory PD Endpoints:* The main estimand is defined with similar attributes as for the primary estimand except that the endpoints are the PD endpoints as listed above.
Immunogenicity	**Immunogenicity Endpoints**
To evaluate the effect of immunogenicity to AL002 on safety, PK and PD biomarkers in participants with early AD	• Incidence of anti-drug antibodies (ADAs).

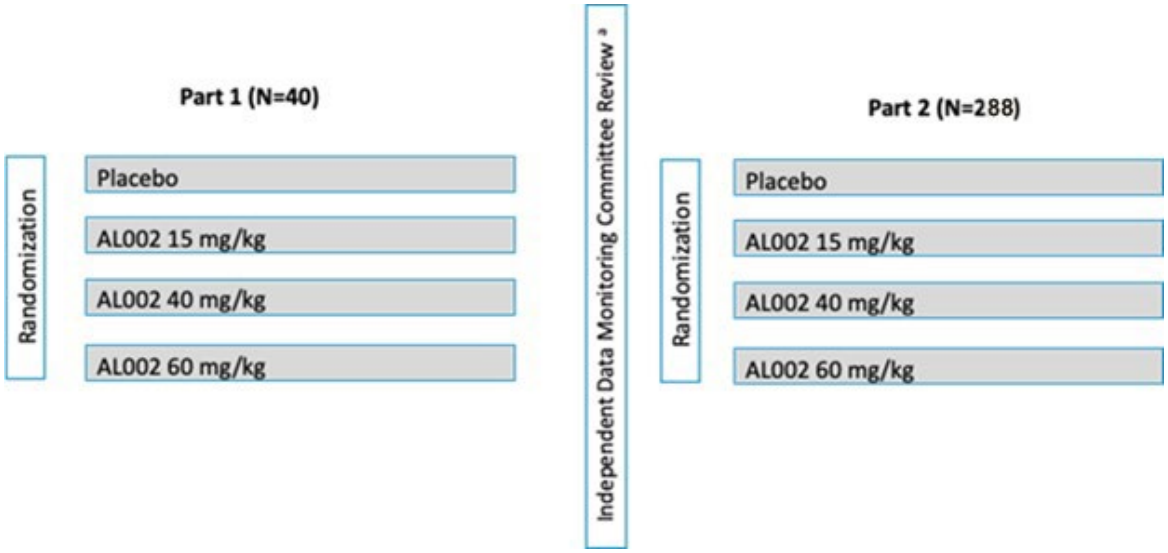
3. STUDY DESIGN

3.1 Study Design

This is a two-part Phase 2, randomized, double-blind, parallel-group, dose-ranging, placebo-controlled study to evaluate the efficacy and safety of AL002 in participants with early AD. The study is a multicenter, global trial that will enroll approximately 328 participants at up to 90 sites in North America, Australia, New Zealand, Europe, and South America.

The study will be conducted in two parts, as outlined in Figure 3-1.

Figure 3-1. Study Design



[a] After at least 40 participants in Part 1 have completed the Day 43 visit, safety, tolerability, and PK data from Part 1 will be reviewed by the independent data monitoring committee (iDMC). Randomization may be paused to allow the iDMC to review data prior to Part 2 commencing. Participants randomized to 40 or 60 mg/kg will be titrated to their assigned dose over 2 or 3 doses, respectively.

3.1.1 Part 1 Description

Part 1 consists of the first approximately 40 participants who receive investigational drug (AL002) or placebo on Day 1 and Day 29 visits. In Part 1, the administration of the first infusion (Day 1) between any 2 participants at any site will be separated by at least 24 hours. After the Day 43 visit, participants in Part 1 will be treated at their current dose and followed according to the same dosing and assessment schedule outlined for Part 2 for the remainder of their study participation (starting at the Week 9 visit). The iDMC will review all safety data from Part 1 when approximately the 20th participant and approximately the 40th participant (minimum of 32nd) complete their Day 43 visit. The Part 1 sample size may be increased if there are higher than expected early dropouts (not attributed to safety) to ensure at least 32 participants complete their Day 43 visit. Part 1 participants will have available safety, tolerability, and PK data at the Day 43 visit, including data from the brain MRI and neurological and ophthalmological examinations reviewed by the iDMC. All participants in Part 1 will receive 2 infusions of investigational drug (1 infusion on Day 1 visit and a second infusion on Day 29 visit), and safety and tolerability assessments on Day 8 (±2 days), Day 15 (±2 days), Day 29 (±2 days), and Day 43 (±2 days) visits. On Day 15 and 43 visits, a brain MRI will be performed; participants with MRI evidence of amyloid-related imaging

abnormality (ARIA) will not be eligible to receive further administration of study drug. Additionally, on Day 43 visit, an ophthalmological examination, neurological examination, and a lumbar puncture (LP) will be performed.

3.1.2 Part 2 Description

Part 2 consists of approximately 288 participants. Each participant in Part 2 will receive up to 96 weeks of treatment. Efficacy, safety, and tolerability assessments will be performed as detailed in the protocol. Brain MRI will be performed prior to dosing at Weeks 5, 9, 13 and 25 visits, and then every 24 weeks. The iDMC will review cumulative safety data approximately every 6 months. Additional brain MRI may be requested by the Sponsor based on review of AEs. The iDMC may convene on an ad-hoc basis, as required, to review cumulative safety data. See the protocol for further details.

3.1.3 Treatment Duration

The total duration of study participation for each participant will be up to approximately 115 weeks. This includes the screening period of up to 8 weeks prior to the optional Predose Baseline visit or to Day 1 visit, an optional Predose Baseline visit of up to 21 days prior to Day 1 visit, a treatment period of a minimum of 48 weeks and a maximum of 96 weeks, a possible final efficacy follow-up (EFU) visit 4 weeks after the last study drug administration, and a mandatory safety follow-up (SFU) visit approximately 8 weeks after the last study drug administration. An EFU visit will be required for a given participant only if a minimum number of weeks have elapsed since the previous efficacy assessments (COAs, fluid and imaging biomarkers) for that participant. Please see the Schedules of Assessments in the protocol for details on when an EFU visit is required.

The treatment period for each participant in this study will be a minimum of 48 weeks and a maximum of 96 weeks, with treatment duration varying for each participant. The earliest randomized participants will have a treatment period of 96 weeks and the last randomized participants will have a treatment period of approximately 48 weeks.

A treatment period termination date (TPTD) is defined as the single, cross-study date that is the end of the treatment period for all participants in the study. The TPTD for all participants in the study will be based on the date when the last randomized participant receives the first dose of study treatment on their Day 1 visit and the TPTD will occur 48 weeks from that date (i.e., the TPTD is the projected Week 49 visit for the last participant randomized). All study sites will be informed of the TPTD when the last randomized participant receives their first dose of study drug, as that will determine when all participants in the study will receive their last dose of study drug.

All participants must have their final visit of their treatment period (whether dosed with study drug or not) on or before the TPTD, and all visits after the TPTD will be follow-up. In the event that the visit window (+5 days) for a given participant falls after the TPTD, it will be modified for this participant such that the visit window will instead end on the TPTD. This will ensure the final visit of the treatment period, for all participants, will be on or before the TPTD.

3.1.4 Treatment Administered

All participants in Part 1 and Part 2 will receive study treatment (placebo, 15 mg/kg AL002, 40 mg/kg AL002, or 60 mg/kg AL002). Study drug administration will begin on Day 1 visit and then will occur once every 4 weeks for the duration of the treatment period according to the Schedules of Assessments in the protocol.

In order to maintain the blind across all dose groups and allow step titration to the higher doses, the starting dose for each participant randomized to receive AL002 will be 15 mg/kg (or placebo) for the first study drug administration on Day 1 visit. For the second study drug administration, the dose will increase to 40 mg/kg for participants randomized to receive 40 mg/kg or 60 mg/kg, while doses in the other 2 groups will remain constant. For the third study drug administration, the dose will increase to 60 mg/kg for participants randomized to receive 60 mg/kg while doses in the other 3 groups will remain constant. The titration algorithm is provided in below Table 3-1.

Table 3-1. Titration Algorithm

Randomized Group	Titration Step 1 Study Day 1	Titration Step 2 Study Day 29 (Week 5)	Titration Step 3 Study Day 57 (Week 9)
AL002 60 mg/kg	AL002 15 mg/kg	AL002 40 mg/kg	AL002 60 mg/kg
AL002 40 mg/kg	AL002 15 mg/kg	AL002 40 mg/kg	AL002 40 mg/kg
AL002 15 mg/kg[a]	AL002 15 mg/kg	AL002 15 mg/kg	AL002 15 mg/kg
Placebo[a]	Placebo (60 mg/kg equivalent)	Placebo (60 mg/kg equivalent)	Placebo (60 mg/kg equivalent)

[a] Participants randomized to receive 15 mg/kg or placebo will not undergo titration.

3.2 Randomization

Participants in Part 1 (approximately 40 participants total) will be randomly assigned on or prior to the Predose Baseline visit (if applicable), or on or prior to the Day 1 visit (if there is no Predose Baseline visit), by stratification on APOE e4 status (e4 carrier vs non-e4 carrier) to receive 15 mg/kg AL002, 40 mg/kg AL002, 60 mg/kg AL002, or placebo in an overall 1:1:1:1 allocation ratio. Participants in Part 2 (approximately 288 participants total) will also be randomly assigned on or prior to the Predose Baseline visit (if applicable) or on or prior to the Day 1 (if there is no Predose Baseline visit) by stratification on APOE e4 status (e4 carrier vs non-e4 carrier) to receive 15 mg/kg AL002, 40 mg/kg AL002, 60 mg/kg AL002, or placebo, using a 1:1:1:1 allocation ratio. An interactive web response system will be used to administer the randomization schedule. Further specific details will be described in the randomization specifications.

3.3 Hypothesis Testing

The null and alternate hypotheses for comparing each of the treatment groups to placebo for the primary estimand 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.

3.4 Interim Analysis

There will be no interim analysis.

3.5 Sample Size

The primary analysis model is a proportional mixed-model for repeated measurements (pMMRM) which estimates an average treatment effect over all the post-baseline visits. Our proposed model estimates the weighted average across the time-varying components. The model provides a clinically meaningful estimation of the treatment benefit averaged across the full duration of the clinical trial, rather than focusing on a single timepoint at the last visit, which may be a random high/low assessment.

To assess the power of the proposed pMMRM, a simulation experiment was conducted using the planned common close design with CDR-SB assessments at baseline, month 6, 12, 18 and 24. Data on the CDR-SB from clinical trials for AD, that are part of a master dataset (Kennedy, Cutter, et al., 2015; Kennedy, Wang, et al., 2015; G. Wang et al., 2015), was used as the basis for assumptions for the simulations. A total of 441 patients with a global baseline CDR score of 0.5 and 1.0 were selected from this master dataset and the mean and covariance matrix were estimated using a mixed-effects model for repeated measures (MMRM). The mean and covariance were then used in simulations to estimate the power of the study. The following table (Table 3-2) shows the power based on the planned primary analysis method (pMMRM), for different sample sizes per group and different treatment effect assumptions, under the common close design using a two-sided 10% significance level. Under the common close design, we have assumed that 22% (per visit), 27% (per visit), 44% (total) and 58% (total) of participants will be missing CDR-SB data at month 6, 12, 18 and 24, respectively, due to dropout and the common close nature of the study design. A total of 5000 simulations were run per scenario.

Table 3-2. Sample Size Simulations

Sample Size	Assumed Treatment Effect [a]		
	0%	**30% Reduction**	**40% Reduction**
60/group	<10%	59%	78%
70/group	<10%	64%	83%

[a] Power based on a two-sided 10% significance level. A total of 5000 simulations were run per scenario.

Based on the above power calculations, 70 participants per group will provide approximately 83% power to detect at least a 40% reduction in the CDR-SB score between any one treatment group and the placebo group. To account for an additional 15 participants who discontinued the study drug prematurely because of the removal of the APOE e4-homozygous participants, 6 participants who were randomized but never received any study drug administration, and 27 participants who prematurely discontinued from the study, a total of 82 participants per group is planned to be randomized. The planned total sample size is therefore approximately 328 participants (approximately 82 participants per group).

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, and protocol violations will be identified and decisions for inclusion and exclusion of participants from the per-protocol analysis set will be made prior to the final database lock and data analysis.

5. ANALYSIS SETS

5.1 All Randomized Set (ARS)

The ARS will include every participant randomized.

All analyses using the ARS will group participants according to the assigned treatment.

5.2 As-Treated Set (ATS)

The ATS will consist of all participants who received any study treatment. All analyses using the ATS will group participants according to the actual treatment received.

If a participant is randomized to any dose level of AL002 and receives any amount of AL002, they will be analyzed at the highest dose level of AL002 received by the participant. Especially for participants who went on the dose titration algorithm (Table 3-1), their actual treatment received will be determined based on their Exposure – IV electronic CRF records and the participant visit dispensing history in the Interactive Response Technology (IRT) system.

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

The AL002-2 study originally included enrollment of participants who were APOE e4 homozygotes (e4/e4). However, further enrollment of participants with this APOE genotype was permanently stopped after the evaluation of safety among the early enrolled participants with e4/e4. Therefore, the primary objective of the study changed to the assessment of AL002 in the participants without e4/e4.

As a result, all analyses will primarily be based on all participants who were randomized, received any study treatment, and are not e4/e4 (non-e4/e4), unless otherwise specified. A limited set of analyses will be provided for the e4/e4 participants as specified in the SAP.

A participant's APOE e4 status and APOE genotype will be determined by the APOE genotype central laboratory data provided by the vendor. If a participant's APOE genotype is not e4/e4, then the participant is not APOE e4-homozygous (i.e., the participant is non-e4/e4).

5.3.1 Full Analysis Set (FAS)

The FAS will consist of all participants who were randomized, received any amount of study drug, and are non-e4/e4. All analyses using the FAS will group participants according to the assigned treatment.

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

5.3.2 Per-Protocol Analysis Set (PPS)

The PPS will consist of all participants in the FAS excluding participants who met either criterion:

- Any participant who did not receive at least 3 doses of study drug (i.e., total doses of study drug < 3),
- Any participant with major protocol deviations due to inclusion/exclusion criteria.

All analyses using the PPS will group participants according to the assigned treatment. This analysis set will be used for supplementary analyses of the primary efficacy endpoint.

5.3.3 Non-e4/e4 Set

The Non-e4/e4 Set will consist of all participants who received any study treatment and are non-e4/e4.

All analyses using the Non-e4/e4 Set will group participants according to the actual treatment received and follow the same rules as described above in the ATS (Section 5.2).

5.3.4 Pharmacokinetic (PK) Set

The PK Set will include all participants in the ATS that received AL002, had at least one post-dose measurable concentration, and are non-e4/e4. The PK Set will only be used for concentration descriptive summary.

All PK summaries using the PK Set will group participants according to the actual treatment received and follow the same rules as described above in the ATS (Section 5.2).

5.4 APOE e4-Homozygous Participants Set (e4/e4 Set)

The e4/e4 Set will consist of all randomized and dosed participants who are e4/e4. In other words, this subset includes e4/e4 dosed participants.

Analyses for this subset will group participants according to the actual treatment received and follow the same rules as described above in the ATS (Section 5.2).

6. SPECIFICATION OF ENDPOINTS AND VARIABLES

6.1 Demographics and Baseline Characteristics

In general, baseline will be defined as the last non-missing assessment, including repeated and unscheduled assessments, prior to the first study treatment administration, unless otherwise specified. If the date of an assessment is on the day of the first study treatment administration and the *chronological* order of the first study treatment administration and the assessment is indeterminate (e.g., because the specific time of the assessment is unknown), the assessment will be used as the baseline, unless otherwise specified. Selection of baseline is specified in Section 7.1.2.

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 will be collected at the Screening visit.

Weight and height will be collected at the Screening visit. Weight will be collected throughout study. Body mass index (BMI) will be calculated as the weight in kg divided by the square of height in meters.

Social history will be collected in the Screening visit. It includes the following information, past and current, regarding the participant: educational attainment, marital status, employment status, tobacco use (smoking, vaping, chewing), alcohol consumption, cannabinoid use and recreational drug use.

Age at AD diagnosis will be calculated from the date of diagnosis and birth year as {(year of diagnosis) – (year of birth)}.

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}. 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 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. If a participant's APOE genotype contains "e4", the participant is considered an e4 carrier (or carrier); otherwise, a non-e4 carrier (or non-carrier).

The PD biomarker assessments will consist of, but are not limited to, blood-based biomarkers, CSF-based biomarkers (when available), and imaging biomarkers and will be collected during screening. Other timing and frequency of all PD biomarker assessments are presented in the Schedules of Assessments in protocol.

Demographic variables will include the following:

- Age (years) 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
  - e4 Carrier
  - Non-e4 carrier
  - Missing (including blank, not reported, unknown, etc.)
- APOE genotype
  - e2/e3
  - e2/e4
  - e3/e3
  - e3/e4
  - e4/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

Baseline social history variables will include the following:

- Marital Status
  - Married
  - Unmarried
  - Widowed
  - Missing (including blank, not reported, unknown, etc.)

- Education
  - Secondary School
  - College or University
  - Post-graduate or Professional
  - None
  - Missing (including blank, not reported, unknown, etc.)
- Employment Status
  - Retired
  - Still working
  - Never worked
  - Missing (including blank, not reported, unknown, etc.)
- Alcohol and its frequency
  - Never
  - Current
    - More than 2 drinks per day
    - 2 or less drinks per day
  - Former
    - More than 2 drinks per day
    - 2 or less drinks per day
  - Missing (including blank, not reported, unknown, etc.)
- Cannabinoids and their usage duration
  - Never
  - Current
    - Duration of usage (years)
  - Former
    - Duration of usage (years)
  - Missing (including blank, not reported, unknown, etc.)
- Recreational drugs and their usage duration
  - Never
  - Current
    - Duration of usage (years)
  - Former
    - Duration of usage (years)
  - Missing (including blank, not reported, unknown, etc.)
- Tobacco and its types
  - Never
  - Current
    - Smoking
    - Chewing
    - Vaping
  - Former
    - Smoking
    - Chewing
    - Vaping
  - Missing (including blank, not reported, unknown, etc.)

- Smoking and its usage duration and daily amount
  - Duration of usage (years)
  - Daily usage (packs)

6.1.2 Medical and Surgical History

Medical and surgical history will be collected on the electronic CRF at the Screening. Medical and surgical history will be coded using the latest version of the medical dictionary for regulatory activities (Medical Dictionary for Regulatory Activities (MedDRA), Version 23 or newer).

6.1.3 Medical and Surgical Treatment Procedures

Medical and surgical treatment procedures will be collected on the electronic CRF. Medical and surgical treatment procedures will be coded using the MedDRA, Version 23 or newer.

6.1.4 Prior and Concomitant Medications/Treatments

A medication will be considered as "*prior*" if the end date of administration is before the start of the first study treatment administration on Study Day 1.

A medication will be considered "*concomitant*" if the end date of administration is after the start of study treatment administration or if the start date is at or after the start of study treatment administration. If the date and time of administration contains partial information such that the attribution of concomitant administration cannot be ruled out, then it will be considered as "*concomitant*". Concomitant medications will be collected at all visits. Medications with end date of 'Ongoing' are considered concomitant.

Any medication with a start date prior to or on the first dose date of study drug and continued after the first dose date or started after the first dose date but prior to or on the last dose date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dose date or the last dose date of study drug will also be considered concomitant. Medications with an end date prior to the first dose date of study drug or a start date after the last dose date of study drug 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 date of first study drug administration 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 study drug end date 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.

6.1.4.1 Uncoded Medication

During interim analysis, uncoded records 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. In the final dataset, all the terms will be coded.

6.1.4.2 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 Efficacy Endpoints

6.2.1 Primary Efficacy Endpoint and Estimands

The primary efficacy endpoint is CFB to all scheduled post-baseline visits (i.e., Week 24, 48, 72 and 96) in CDR-SB.

6.2.1.1 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 6-1 (O'Bryant et al., 2010), with a higher score indicating a greater cognitive deficit.

Table 6-1. 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

CDR-SB Range	Staging Category
9.5 - 15.5	Moderate dementia
16.0 - 18.0	Severe dementia

6.2.1.2 Primary Estimand for Primary Efficacy Endpoint

- Treatment condition: while on study treatment regardless of other interventions.
- Target population: adult participants with early AD, excluding APOE e4/e4 participants as defined by the protocol inclusion/exclusion criteria.
- Primary endpoint: CFB in CDR-SB score to Weeks 24, 48, 72, and 96.
- 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.

6.2.1.3 Supportive Estimand for Primary Efficacy Endpoint

The supportive estimand for the primary efficacy endpoint is defined with the same attributes as in the primary estimand for the primary efficacy endpoint 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 primary estimand for the primary efficacy endpoint, 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.

6.2.2 Secondary Efficacy Endpoints and Estimands

The secondary efficacy endpoints include:

- CFB to Week 24, 48, 72, and 96 in MMSE
- CFB to Week 24, 48, 72, and 96 in RBANS
- CFB to Week 24, 48, 72, and 96 in ADAS-Cog13
- CFB to Week 24, 48, 72, and 96 in ADCS-ADL-MCI
- CFB to Week 24, 48, 72, and 96 in ADCOMS
- CFB to Week 24, 48, 72, and 96 in modified iADRS

6.2.2.1 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.

6.2.2.2 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.

6.2.2.3 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.

6.2.2.4 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 of 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.

6.2.2.5 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 the Wold's partial least regression (PLS) model using the corresponding PLS coefficients in the fitted model (Table 6-2) and has shown improved sensitivity to clinical decline in the 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 6-2).

The ADCOMS will be scored for each participant using the components/items and their PLS coefficients in Table 6-2, 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 across 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 7.1.3.1.

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

Table 6-2. 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

Scale	Item Name	Item ID	PLS Coefficients
	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).

6.2.2.6 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), with higher scores indicating better cognitive and functional performance and lower scores suggesting greater impairment (Wessels et al., 2015) (Wessels et al., 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 the total scores from the ADAS-Cog13 and the ADCS-ADL-MCI. The modified iADRS score is calculated as follows:

$$\text{Modified iADRS Score} = [-1(\text{ADAS-Cog13}) + 85] + \text{ADCS-ADL-MCI}$$

The modified iADRS score will first be calculated based on the total scores of ADAS-Cog13 and ADCS-ADL-MCI on 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. And the maximum study day of the total score of ADAS-Cog13 and the total score of ADCS-ADL-MCI used to calculate the modified iADRS score 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 components (that contribute to the composite score) or the composite score, please refer to Section 7.1.3.1.

6.2.2.7 Estimands for Secondary Efficacy Endpoints

The primary and supportive estimands for each of the secondary efficacy endpoints are defined with the same attributes as in the primary and supportive estimands except that it is endpoint specific and population-level summary specific.

6.3 Safety Endpoints and Variables

Safety variables include the following (refer to Section 7.1.1.2.2 for analysis visit definitions):

- AE, AESI, and SAE
- C-SSRS at Week 24, Week 48, Week 72, Week 80, and Week 96
- CFBs in hematology and chemistry at Week 2, Week 4, Week 6, Week 12, Week 28, Week 40, Week 52, and Week 80
- CFBs in urinalysis at Week 2, Week 4, Week 6, Week 28, Week 52, and Week 80
- CFBs in coagulation at Week 4, Week 44, and Week 68
- CFBs in ECG at Week 4, Week 12, Week 24, Week 48, and Week 80
- CFBs in vital signs at all scheduled post-baseline visits
- MRI abnormalities at Week 2, Week 4, Week 8, Week 12, Week 24, Week 48, Week 72, and Week 96
- CFBs in neurological examination at Week 6, Week 12, Week 28, Week 52, and Week 80
- CFBs in ophthalmological examination at Week 6, Week 16, Week 32, Week 48, and Week 72
- CFBs in physical exam at Week 12, Week 28, Week 52, and Week 80

6.3.1 Extent of Exposure to Study Drug, Duration of Study and Treatment Compliance

All participants will receive intravenous (IV) administration of either AL002 or placebo on Study Day 1 and then q4w (every 4 weeks) over a 48-week to 96-week period, according to the Schedule of Assessments in the protocol.

Study treatment administration data will be summarized by duration of exposure to study drug, number of doses received, and treatment compliance.

Duration of Exposure

Duration of exposure to study drug (day) is defined as the total number of days a participant is exposed to any study drug and will be calculated as the total number of days from the first dose date (Study Day 1) to the earliest date of the last dose date + 28 days and the death date + 1 day, regardless of any temporary interruptions in study drug administration, i.e., duration of exposure to study drug (day) = min(last dose date – first dose date + 28, death date – first dose date + 1). The last dose date is defined in Section 7.1.1.1. 28 days (q4w) is the study treatment administration (IV) interval.

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

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

Participant-years of exposure are defined as the participants' exposure to study drug in years, which is calculated as the sum of each participant's duration of exposure to study drug in days divided by 365.25.

Duration of Study

Duration of study (day) is defined as the total number of days a participant is on the study and will be calculated as the total number of days from the first dose date (Study Day 1) to the last study date, i.e., duration of study (day) = last study date – first dose date + 1). The last study date is the latest date that marks the end of a participant's participation in the study.

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

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

If the last study date on the Study Completion page is missing, or if a participant is lost to follow-up, the latest visit date will be used.

Number of Doses

The number of doses of study drug is defined as the total number of doses 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 (either placebo or AL002) while they are on study treatment across all planned study days, up to the date of withdrawal, if participant discontinued study drug early.

The formula for calculation is as follows:

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

6.3.2 Adverse Events

All AEs will be collected after the participant signs the informed consent. 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.

6.3.2.1 Treatment-Emergent Adverse Events

- If both the start time of the AE and the time of the first study drug administration are available, an AE is considered a TEAE if its start date and time are after the first study drug administration start time and no later than 90 days after the last dose date. The last dose date is defined in Section 7.1.1.1.
- If either the start time of the AE or the time of the first study drug administration is unavailable, an AE is considered a TEAE if its start date is on or after the first dose date and no later than 90 days after the last dose date. Handling of incomplete dates is specified in Section 6.3.2.6.

6.3.2.2 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 Grade 2 or higher

6.3.2.3 Serious Adverse Events

SAEs will be identified and captured as SAEs if AEs met the definitions of SAEs that were specified in the protocol.

6.3.2.4 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.

6.3.2.5 Relationship of Adverse Events to Radiotracers

A listing will be provided for TEAEs that are related to radiotracers.

6.3.2.6 Incomplete Dates

If the start date of the AE is incomplete and the AE end date is not prior to the first dose date of study drug, 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 study drug, 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 date of the last dose of study drug.

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 study drug, 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 study drug 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 date:

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

For partial end date:

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

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

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.

6.3.2.7 Deaths

Deaths will be captured as SAEs (i.e., SAEs result in death regardless whether it is treatment-emergent or not) according to the methods described above.

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

Two versions of the C-SSRS will be used in this 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 will be administered on 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.

6.3.4 Laboratory Data

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

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.

The tests performed are shown below in Table 6-3.

6.3.4.1 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 6-3. 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; WOCBP=woman of childbearing potential.

6.3.4.2 Potential Serious Hepatotoxicity

Following Hy's law, potential serious hepatotoxicity is defined as ALT or AST > 3 x ULN and total bilirubin > 2 x ULN at any time post-baseline, not necessarily concurrent.

6.3.5 Electrocardiogram (ECG)

Triplicate 12-lead ECGs including heart rate, QRS duration, QT interval corrected using the Fridericia formula (QTcF) interval, RR interval and result interpretation will be captured on the electronic CRF. Triplicate 12-lead ECGs will be obtained approximately 1 minute apart at the Screening and before blood draws (predose) and 60 to 90 minutes after the end of infusion at scheduled visits (refer to the protocol for scheduled visits). The investigator will assess and

document whether the ECG is "Normal", "Abnormal not clinically significant", "Abnormal clinically significant" or "Not evaluable". In addition, triplicate ECG tracings from Day 1 and Week 25 or Week 49 for approximately 100 consecutive participants will be read by a core ECG laboratory. Results from centrally read ECGs will not be captured on the electronic CRF but provided by a vendor and will be analyzed separately.

ECG parameters will include the following:

- Heart Rate (beats/min)
- QRS duration (msec)
- RR Interval (msec)
- QTcF Interval (msec)
- Interpretation

6.3.6 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. Weight will be collected at scheduled visits (refer to the protocol 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)

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

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

6.3.7.1 ARIA-E

6.3.7.1.1 *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.

6.3.7.1.2 *Severity Definition*

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

6.3.7.1.3 *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.

6.3.7.1.4 *Time to First Occurrence and Recurrence Definition*

- Time to the first occurrence is defined as the number of days from the first dose date to the exam date of the first 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.

6.3.7.2 New ARIA-H

6.3.7.2.1 *Event Definition*

A new event of ARIA-H is defined as an MRI scan at a post-baseline visit if any of the criteria below as captured on its BMW is satisfied:

- CFB in the number of microhemorrhages > 0, or
- CFB in the number of areas of leptomeningeal hemosiderosis (also referred to as superficial siderosis) > 0, or
- Presence of macrohemorrhages.

6.3.7.2.2 *Severity Definition*

Individual radiographic severity for microhemorrhages, leptomeningeal hemosiderosis and macrohemorrhages is defined in Table 6-4. ARIA-H radiographic severity is defined as the worst individual radiographic severity among microhemorrhages, leptomeningeal hemosiderosis and macrohemorrhages for an MRI scan as captured in its BMW. If any macrohemorrhages are present at an MRI scan, then the ARIA-H radiographic severity is severe. If macrohemorrhages are absent at an MRI scan, then the worse severity between microhemorrhages and leptomeningeal hemosiderosis will be the ARIA-H radiographic severity. For example, if there are 4 incident microhemorrhages, 1 incident areas of leptomeningeal hemosiderosis and no presence of macrohemorrhages on a BMW, ARIA-H is rated as "Moderate".

Table 6-4. Definition for Individual Radiographic Severity related to ARIA-H

Incident (CFB) Findings	Mild	Moderate	Severe
Number of microhemorrhages	1-4	5-9	10 or more
Areas of leptomeningeal hemosiderosis	–	1	2 or more
Presence of macrohemorrhages	–	–	Yes

6.3.7.2.3 *Time to First Occurrence Definition*

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

6.3.8 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 protocol for scheduled visits). CFBs abnormalities should be recorded at each subsequent neurologic examination. New or worsened abnormalities should be recorded as an AE on the AE electronic CRF if considered clinically significant in the Investigator's opinion.

6.3.9 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 protocol for scheduled visits). CFBs abnormalities are recorded at each subsequent ophthalmological examination. New or worsened abnormalities should be recorded as AE.

6.3.10 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.

6.3.11 Other Safety Assessments

6.3.11.1 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 protocol for scheduled visits).

6.3.11.2 COVID-19

Impact of coronavirus disease 2019 (COVID-19) on consent, scheduled visits, essential on-site assessments and remote visits (via phone or video), COVID-19 related AEs and participant withdrawals will be collected throughout the study.

6.4 Pharmacokinetic (PK) Endpoints

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

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, YKL-40
- CFBs in levels of biomarkers related to AD pathology in CSF and/or plasma including but not limited to Aβ40, Aβ42, pTau, 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 PET (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
- Titer results of ADAs

7. STATISTICAL ANALYSIS

7.1 General Data Handling Rules and Definitions

All analyses will combine data from all participants in Part 1 and Part 2, unless otherwise specified.

Unless otherwise specified, when specifying for summaries and analyses, "treatment group" refers to each individual AL002 15 mg/kg, 40 mg/kg, and 60 mg/kg treatment group, and the placebo group. "AL002 40 and 60 mg/kg combined group" refers to the group pooling AL002 40 mg/kg and 60 mg/kg treatment groups. "Total AL002 group" refers to the group pooling AL002 15 mg/kg, 40 mg/kg, and 60 mg/kg treatment groups. And "overall" refers to the group pooling AL002 15 mg/kg, 40 mg/kg, and 60 mg/kg treatment groups, and the placebo group.

All assessments will be provided in respective by-participant data listings, except data collected only for confirmation of study entry criteria and for study administrative purposes. If any randomized 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 all participants in the ARS and sorted by randomized treatment, actual treatment, 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 within the participant. Age, sex at birth, race, and ethnicity will be included in the listings.

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 maintained as missing, unless specified in Section 7.4.1.

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 will be designated as **Study Day 1**. Study days for other visits will be calculated as follows:

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

The **last dose date** of study drug will be the date of last dose collected on the Study Drug Completion electronic CRF or the date of last non-missing study drug administration record collected on the Exposure – IV electronic CRF, whichever occurs later.

7.1.1.2 Analysis Visit Window Definitions

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 Visit Week 24 in the SAP, and nominal Week 49 in the protocol is Analysis Visit Week 48 in the SAP.

7.1.1.2.1 *Efficacy Data*

Efficacy endpoints are scheduled to be performed or collected at nominal visits per protocol: Screening, Week 25, Week 49, Week 73, Week 97, early termination (ET), and EFU (only collected if COA is not performed or collected within 12 weeks since the last COA collection). 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 7-1.

Efficacy data will be summarized based on the analysis visits (hereinafter may be referred to as "visit"), when applicable.

Table 7-1. Analysis Visit Windows for Efficacy Assessments

Nominal Visit per Protocol	Targeted Day of Nominal Visit (Based on Study Day)	Analysis Visit	Analysis Visit Window (Based on Study Day)
Screening Phase		Baseline[b]	≤ 1
Screening	-		
Treatment Phase			
Week 1 [a]	1		
Week 25	169	Week 24	[2, 253]
Week 49	337	Week 48	[254, 421]
Week 73	505	Week 72	[422, 589]
Week 97	673	Week 96	≥ 590

[a] COAs are scheduled to be performed/collected prior to dosing.
[b] Baseline for efficacy is defined in Section 7.1.2.

7.1.1.2.2 *Safety and Pharmacokinetic Data*

Unless otherwise specified, for safety and PK data, the upper bound of a post-baseline analysis visit (except for "> 90 Day 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.

Analysis visit windows for the safety and PK data are defined in a similar manner as those for the efficacy parameters. 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 Table 7-2 to Table 7-14.

Table 7-2. Analysis Visit Windows for C-SSRS Assessments

Analysis Visit	Target Day	Analysis Visit Window (Based on Study Day)
Baseline	1	≤ 1
Week 24	169	[2, 253]
Week 48	337	[254, 421]
Week 72	505	[422, 533]
Week 80	561	[534, 617]
Week 96	673	≥ 618

Table 7-3. Analysis Visit Windows for Hematology, Chemistry and Urinalysis Assessments

Analysis Visit		Target Day	Analysis Visit Window (Based on Study Day)
Baseline		-	≤ 1
Week 2		15	[2, 22]
Week 4		29	[23, 36]
Week 6		43	[37, 64]
Week 12 (Hematology and Chemistry only)		85	[65, 141]
Week 28	Hematology and Chemistry	197	[142, 239]
	Urinalysis		[65, 323]
Week 40 (Hematology and Chemistry only)		281	[240, 323]
Week 52		365	[324, 463]
Week 80		561	≥ 464

Table 7-4. Analysis Visit Windows for Coagulation Assessments

Analysis Visit	Target Day	Analysis Visit Window (Based on Study Day)
Baseline	-	≤ 1
Week 4	29	[2, 169]
Week 44	309	[170, 393]
Week 68	477	≥ 394

Table 7-5. Analysis Visit Windows for ECG Assessments

Analysis Visit [1]	Target Day	Analysis Visit Window (Based on Study Day)
Baseline	-	≤ Day 1 Predose
Day 1 Postdose	1	Day 1 Postdose
Week 4	29	[2, 57]
Week 12	85	[58, 127]
Week 24	169	[128, 253]
Week 48	337	[254, 449]
Week 80	561	≥ 450

[1] 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 7.1.4.3.

Table 7-6. Analysis Visit Windows for Central ECG Assessments

Analysis Visit [1]	Target Day	Analysis Visit Window (Based on Study Day)
Baseline	-	≤ Day 1 Predose
Day 1 Postdose	1	Day 1 Postdose
Week 24	169	[2, 253]
Week 48	337	≥ 254

[1] 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 7.1.4.3.

Table 7-7. Analysis Visit Windows for Weight

Analysis Visit	Target Day	Analysis Visit Window (Based on Study Day)
Baseline	-	≤ 1
Week 4	29	[2, 43]
Week 8	57	[44, 71]
Week 12	85	[72, 99]
Week 16	113	[100, 127]
Week 20	141	[128, 155]
Week 24	169	[156, 183]
Week 28	197	[184, 211]
Week 32	225	[212, 239]
Week 36	253	[240, 267]
Week 40	281	[268, 295]
Week 44	309	[296, 323]
Week 48	337	[324, 351]
Week 52	365	[352, 379]
Week 56	393	[380, 407]
Week 60	421	[408, 435]
Week 64	449	[436, 463]
Week 68	477	[464, 491]
Week 72	505	[492, 519]
Week 76	533	[520, 547]
Week 80	561	[548, 575]
Week 84	589	[576, 603]
Week 88	617	[604, 631]
Week 92	645	[632, 659]
Week 96	673	≥ 660

Table 7-8. Analysis Visit Windows for Vital Signs

Analysis Visit[1]	Target Day	Analysis Visit Window (Based on Study Day)
Baseline	-	≤ Day 1 Predose
Day 1 Postdose	1	Day 1 Postdose
Week 2	15	[2, 22]
Week 4	29	[23, 36]
Week 6	43	[37, 50]
Week 8	57	[51, 71]
Week 12	85	[72, 99]
Week 16	113	[100, 127]
Week 20	141	[128, 155]
Week 24	169	[156, 183]
Week 28	197	[184, 211]
Week 32	225	[212, 239]
Week 36	253	[240, 267]
Week 40	281	[268, 295]
Week 44	309	[296, 323]
Week 48	337	[324, 351]
Week 52	365	[352, 379]
Week 56	393	[380, 407]
Week 60	421	[408, 435]
Week 64	449	[436, 463]
Week 68	477	[464, 491]
Week 72	505	[492, 519]
Week 76	533	[520, 547]
Week 80	561	[548, 575]
Week 84	589	[576, 603]
Week 88	617	[604, 631]
Week 92	645	[632, 659]
Week 96	673	≥ 660

[1] 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 7.1.4.3.

Table 7-9. Analysis Visit Windows for MRI Assessments

Analysis Visit	Target Day	Analysis Visit Window (Based on Study Day)
Baseline	-	≤ 1
Week 2	15	[2, 22]
Week 4	29	[23, 36]
Week 6	43	[37, 50]
Week 8	57	[51, 71]
Week 12	85	[72, 127]
Week 24	169	[128, 253]
Week 48	337	[254, 421]
Week 72	505	[422, 589]
Week 96	673	≥ 590

Table 7-10. Analysis Visit Windows for Ophthalmological Examination

Analysis Visit	Target Day	Analysis Visit Window (Based on Study Day)
Baseline	-	≤ 1
Week 6	43	[2, 78]
Week 16	113	[79, 169]
Week 32	225	[170, 281]
Week 48	337	[282, 421]
Week 72	505	≥ 422

Table 7-11. Analysis Visit Windows for Neurological Examination and Physical Examination

Analysis Visit		Target Day	Analysis Visit Window (Based on Study Day)
Baseline		-	≤ 1
Week 6 (Neurological Examination only)		43	[2, 64]
Week 12	Neurological Examination	85	[65, 141]
	Physical Examination		[2, 141]
Week 28		197	[142, 281]
Week 52		365	[282, 463]
Week 80		561	≥ 464

Table 7-12. Analysis Visit Windows for ADA (Serum) Assessments

Analysis Visit	Target Day	Analysis Visit Window (Based on Study Day)
Baseline	-	≤ 1
Week 2	15	[2, 22]
Week 4	29	[23, 36]
Week 6	43	[37, 50]
Week 8	57	[51, 85]
Week 16	113	[86, 141]
Week 24	169	[142, 211]
Week 36	253	[212, 295]
Week 48	337	[296, 379]
Week 60	421	[380, 463]
Week 72	505	[464, 547]
Week 84	589	[548, 631]
Week 96	673	≥ 632

Table 7-13. Analysis Visit Windows for PK (Serum) Assessments

Analysis Visit	Target Day	Analysis Visit Window (Based on Study Day)
Day 1	1	≤ 1
Week 1	8	[2, 12]
Week 2	15	[13, 22]
Week 4	29	[23, 36]
Week 6	43	[37, 50]
Week 8	57	[51, 71]
Week 12	85	[72, 99]
Week 16	113	[100, 141]
Week 24	169	[142, 211]
Week 36	253	[212, 295]
Week 48	337	[296, 379]
Week 60	421	[380, 463]
Week 72	505	[464, 547]
Week 84	589	[548, 631]
Week 96	673	≥ 632

Table 7-14. Analysis Visit Windows for PK (CSF) Assessments

Analysis Visit	Target Day	Analysis Visit Window (Based on Study Day)
Baseline	1	≤ 1
Week 6	43	[2, 190]
Week 48	337	[191, 421]
Week 72	505	≥ 422

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. Biomarker data will be allocated to analysis visits corresponding to the analysis visit window intervals in which they fall in as specified in Table 7-15 to Table 7-19.

Table 7-15. Analysis Visit Windows for PD Plasma Biomarker Assessments

Analysis Visit	Target Day	Analysis Visit Window (Based on Study Day)
Baseline	1	≤ 1
Week 1	8	[2, 12]
Week 2	15	[13, 22]
Week 4	29	[23, 36]
Week 6	43	[37, 50]
Week 8	57	[51, 71]
Week 12	85	[72, 99]
Week 16	113	[100, 141]
Week 24	169	[142, 211]
Week 36	253	[212, 295]
Week 48	337	[296, 379]
Week 60	421	[380, 463]
Week 72	505	[464, 547]
Week 84	589	[548, 631]
Week 96	673	≥ 632

Table 7-16. Analysis Visit Windows for CSF Biomarker Assessments

Analysis Visit	Target Day	Analysis Visit Window (Based on Study Day)
Baseline	1	≤ 1
Week 6	43	[2, 190]
Week 48	337	[191, 421]
Week 72	505	[422, 589]
Week 96	673	≥ 590

Table 7-17. Analysis Visit Windows for Amyloid PET Assessments

Analysis Visit	Target Day	Analysis Visit Window (Based on Study Day)
Baseline	1	≤ 1
Week 48	337	[2, 505]
Week 96	673	≥ 506

Table 7-18. Analysis Visit Windows for Tau PET Assessments, True Baseline*

Analysis Visit	Target Day	Analysis Visit Window (Based on Study Day)
Baseline	1	≤ 1
Week 48	337	[2, 421]
Week 72	505	[422, 589]
Week 96	673	≥ 590

*True baseline: baseline corresponds to the pre-dose visit (prior to dosing).

Table 7-19. Analysis Visit Windows for Tau PET Assessments, Redefined Baseline (Sensitivity Analysis)*

Analysis Visit	Target Day	Analysis Visit Window (Based on Study Day)
Baseline_R	1	≤ Day 1 Predose, if it exists. If not, then day of Week_R 48 non-missing result (up to Day 421)
Week_R 48	337	[2, 421]
Week_R 72	505	[422, 589]
Week_R 96	673	≥ 590

*Redefined baseline: baseline corresponds to either the pre-dose visit (prior to dosing) if the pre-dose Tau PET scan is evaluable, or 1st postdose visit if the pre-dose Tau PET scan is missing.

7.1.2 Selection of Data for Baseline

The baseline value will be chosen based on the rules specified below, 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 Study Day 1.

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

For participants who didn't have Study Day 1 (i.e., never received study drug administration), their last data collected at the nominal visit of Screening or "Week 01 D01" (for cases when the extension of screening period was approved by the Sponsor) will be used as the baseline values if needed (e.g., summaries of Demographics and Baseline Characteristics on All Randomized Set).

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 baseline value will be the last non-missing and evaluable value prior to 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 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 will not be considered candidates for the baseline value and will be assigned the analysis visit "Day 1 Postdose" (Table 7-5, Table 7-6 and Table 7-8) when applicable.

If multiple non-missing and evaluable records occur on the same day that is closest to Study Day 1 (not on Study Day 1), or on 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”).

For participants who didn’t have Study Day 1 (i.e., never received study drug administration), their last data collected at the nominal visit of Screening, “Predose Baseline”, or “Week 01 D01” will be used as the baseline values if needed.

7.1.2.3 Tau PET Measurement

Two definitions for baseline will be used for Tau PET (refer to Table 7-26 for analysis scope for PD biomarkers).

- *True baseline*: evaluable Tau PET scan result at Pre-dose Baseline visit prior to Study Day 1. If the Tau PET scan is not performed at the Pre-dose Baseline visit, then the baseline value is set to missing.
- *Redefined baseline*: evaluable Tau PET scan result at Pre-dose Baseline visit prior to Study Day 1 if available or the first evaluable post-dose Tau PET scan result if pre-dose Tau PET scan is missing.

True baseline will be used in the main analyses for CFB. Redefined baseline will be used in the sensitivity analyses for CFB.

For participants who never received study drug administration, but were randomized, their data collected at the Screening visit will be used as the baseline value if needed (e.g., summaries of baseline characteristics on the ARS).

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., 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.

For composite efficacy endpoints (ADCOMS and modified iADRS):

If all of the individual components have no more than one value on the same day, then the composite score is first calculated based on all the individual components (one per component) 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 values 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 values 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 values 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 record with the worst value 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 value 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 value 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 measurement time points (predose, post-infusion, or "Not Applicable") on a study drug administration day, the following rules apply for assigning the measurement time points, 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 the assessments collected at a post-Study-Day-1 scheduled visit, in which study drug is administered per the Schedules of Assessments in the protocol, 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 the post-Study-Day-1 visits in which study drug is not administered per the Schedules of Assessments in the protocol, including Week 3 (vital signs only), Unscheduled, EFU, SFU, and ET, "Not Applicable" will be assigned as the measurement time point.

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

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

7.1.4.3 Handling of Baseline 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 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

The number of participants screened, the number (percent) of participants who failed screening, and the reasons for screen failure will be summarized. A summary of participant enrollment will be provided by treatment group, AL002 40 and 60 mg/kg combined group, total AL002 group, and overall for each country, as well as for each investigator within a country. The summary will present the number and percentage of participants enrolled. For each column, the denominator for the percentage calculation will be the total number of participants analyzed for that column.

The randomization schedule used for the study will be listed.

A summary of participant disposition will be provided by treatment group, AL002 40 and 60 mg/kg combined group, total AL002 group, and overall. This summary will group participants according to the assigned treatment for all analysis sets. This summary will present the number of participants screened, the number of participants randomized, and the number of participants in each of the categories listed below:

- ARS
  - Randomized but never dosed
- ATS
  - Completed study drug
  - Discontinued study drug
  - Reasons for premature discontinuation of study drug
  - Completed study
    - Rolled over into LTE
    - Did not roll over into LTE
  - Discontinued study
  - Reasons for premature discontinuation of study
- Non-e4/e4 Set
  - Completed study drug
  - Discontinued study drug
  - Reasons for premature discontinuation of study drug
  - Completed study
    - Rolled over into LTE
    - Did not roll over into LTE
  - Discontinued study
  - Reasons for premature discontinuation of study
- e4/e4 Set
  - Completed study drug
  - Discontinued study drug
  - Reasons for premature discontinuation of study drug
  - Completed study
    - Rolled over into LTE
    - Did not roll over into LTE
  - 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.

The following by-participant data listings will be provided by participant ID number in ascending order to support the above summary tables:

- Reasons for premature study drug or study discontinuation for the ARS,
- Reasons for screen failure for all screened participants,
- Reason why a participant is excluded from a specific analysis set (except for the Non-e4/e4 Set and e4/e4 Set) for the ARS.

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 protocol deviations will be grouped by treatment group, AL002 40 and 60 mg/kg combined group, total AL002 group, and overall for the ARS. A by-participant data listing of all significant protocol deviations including categorization of deviations will be provided for the ARS as well.

7.3 Demographics and Baseline Characteristics

7.3.1 Demographics, Baseline Characteristics, and Medical History

Demographics, baseline characteristics, social history, medical history, and medical and surgical treatment procedures will be summarized by treatment group, AL002 40 and 60 mg/kg combined group, total AL002 group, and overall. Demographics and baseline characteristics will be summarized for the ARS, FAS, and the Non-e4/e4 Set, respectively. Social history, medical history, and medical and surgical treatment procedures will be summarized for the ARS and the Non-e4/e4 Set, respectively. By-participant data listings will be presented for the ARS.

7.3.2 Prior and Concomitant Medications

Prior and concomitant medications will be summarized for the Non-e4/e4 Set.

Prior 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, total AL002 group, and overall.

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 total AL002 group.

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. Each 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 prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-participant data listing sorted by randomized treatment, actual treatment, participant ID number and administration date in chronological order.

7.4 Efficacy Analyses

The FAS will be used for all efficacy analyses, except for the analyses specified in Section 7.4.1.5, unless otherwise specified.

The primary estimand as described in Section 6.2.1.2 will be used for all efficacy analyses, except for the analyses specified in Section 7.4.1.5 which are based on the supportive estimand, and unless otherwise specified.

Missing data will be assumed missing at random (MAR) for all efficacy analyses, except for the analyses specified in Section 7.4.1.4, and unless otherwise specified. Sensitivity analysis to assess the impact of the missingness assumption will be performed using a Pattern Mixture Model (PMM) as described in Section 7.4.1.4.

For each continuous efficacy endpoint, the number of participants with efficacy outcomes, mean, SD, median, Q1, Q3, min, and max, at baseline and each scheduled post-baseline visit, along with CFB and PCFB to each scheduled post-baseline visit, will all be reported and accompany the estimates from the inferential statistical models. The same applies to subgroups specified in Section 7.4.3.

Unless otherwise indicated, all statistical tests will be 1-sided. However, 2-sided p-values will be reported for all tests. A significance level of 0.05 (1-sided) will be used for primary endpoint, with significance achieved if the 2-sided p-value is less than 0.10, and in the direction of indicating more efficacy for non-placebo than for placebo.

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, separately for each estimand.

7.4.1 Analyses of Primary Efficacy Endpoint

Participants in the FAS who have a baseline value and at least one post-baseline value for the primary endpoint are included in the analysis.

7.4.1.1 Primary Efficacy Analysis

The primary analysis will use a pMMRM approach (G. Wang et al., 2022). The details of the pMMRM are presented below. 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 (Table 7-20).

Let y_{ijk} denote the longitudinal assessments for participant i at time j for treatment group k, $i = 1, 2, \ldots, n_k$, $j = 0, 1, \ldots, m_i$, and $k = 1, 2, 3, 4$ represents the placebo group and one of the treatment groups. Specifically, let $k = 2$ denote the treatment group of AL002 15 mg/kg; $k = 3$ denote the treatment group of AL002 40 mg/kg; $k = 4$ denote the treatment group of AL002 60 mg/kg.

The marginal pMMRM which evaluates the treatment effect of the 3 treatment groups simultaneously can be written as:

$$\Delta y_{ijk} = \beta_0(y_{i0k} - \bar{y}_0) + \Delta_{j1}(1 - \theta_k) + \varepsilon_{ijk}$$

where Δy_{ijk} is the individual change from the baseline y_{i0k} and is calculated as $y_{ijk} - y_{i0k}$ for $j = 1, \ldots, m_i$. β_0 is an unknown parameter which represents the association between y_{i0k} and Δy_{ijk}. $\bar{y}_0$ is the marginal mean of the baseline values of both the treatment groups and the placebo group, and the inclusion of $\bar{y}_0$ enables the model to provide a treatment effect adjusted for the baseline value. $\bar{y}_0$ is the arithmetic mean of the baseline values of the treatment groups and the placebo group when the design is balanced (e.g., equal sample size for both groups); and is the marginal mean when the design is unbalance (e.g., missing data lead to different sample size in the two groups). For unbalanced design, $\bar{y}_0$ is the same as the one used in the MMRM least square mean estimation and can be obtained through the MMRM model. Parameters (to be estimated) include Δ_{j1}, the mean CFB for the placebo group at time j for $j \geq 1$, θ_k, the proportional treatment effect for group k with $\theta_k = 0$ for the placebo group, and ε_{ijk}, the within-participant error, which is assumed to follow a multivariate normal distribution:

$\mathrm{N}\left(\begin{pmatrix}0\\0\\\vdots\\0\end{pmatrix}, \boldsymbol{\Sigma}_{m_i \times m_i}\right)$, where $\boldsymbol{\Sigma}$ is an unstructured variance-covariance matrix and m_i is the number of repeated post-baseline measures for participant i.

If the treatment has no effect at all, then the primary endpoint y_{ijk} will progress at the same rates after baseline for the treatment group and the placebo group, leading to $\theta_k = 0$; if the treatment completely stops the disease progression, then y_{ijk} will not progress after the baseline in the treatment group, leading to $\theta_k = 1$; if the treatment worsens the disease progression, then y_{ijk} will progress faster after the baseline in the treatment group than that in the placebo group, leading to $\theta_k < 0$; and if the treatment slows the disease progression, then y_{ijk} will progress slower after the baseline in the treatment group than that in the placebo group, leading to $\theta_k > 0$.

Table 7-20. Comparisons of Statistical Models

Models	Linearity[a]	Time Variable	Treatment Effect	Extended Follow-up
MMRM	No	Categorical	Non-proportional	Yes[b]
pMMRM	No	Continuous/Categorical	Proportional	Yes

[a] refer to the assumption between time as a continuous variable and outcome variable.
[b] when using an MMRM model to obtain estimates at a specific key timepoint, data beyond the key timepoint of interest don't directly contribute to the statistical inference at the key timepoint.

Like MMRM, the parameters in the marginal pMMRM model can be estimated using the (restricted) maximum likelihood method.

The unstructured covariance matrix will be used to model within-participant variance and covariance. The estimates of Δ_{j1}, β_0 and $\boldsymbol{\Sigma}$ from MMRM will be used as the initial values of pMMRM to facilitate model convergence. If the unstructured covariance matrix results in a lack of convergence, the following structures 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 Kenward-Roger method will be used to calculate the denominator degrees of freedom for the test of fixed effects and adjusted standard errors. If the pMMRM that models all three treatment groups simultaneously fails to converge after exploring all the above options, pMMRM will be applied to each treatment group to estimate the treatment effect for each dose separately.

The estimated proportional treatment effect and its 90% and 95% CIs will be reported from the final fitted model.

Additionally, the same analysis described above will be repeated with the following groups in the model: AL002 15 mg/kg group, AL002 40 and 60 mg/kg combined group, and placebo group. All statistics described above from fitting the model will be reported only for the AL002 40 and 60 mg/kg combined group (or its comparison to placebo).

7.4.1.1.1 *Multiplicity Adjustment for Primary Efficacy Endpoint*

For the primary efficacy endpoint, if one single multivariate pMMRM model has a convergence issue after trying all the covariance structure stated above (Section 7.4.1.1), then each dose of AL002 will be compared to placebo in a pairwise manner. To adjust for multiplicity, the fixed sequence procedure (FSP) will be used (Westfall & Krishen, 2001). A fixed testing order will be used starting with the AL002 40 and 60 mg/kg combined group, followed by the highest dose, then followed by the next lower dose, and then the next lower dose. All tests will be performed at the 1-sided 0.05 level following this pre-specified order. Once one null hypothesis is not rejected, all subsequent tests will be exploratory in nature.

7.4.1.2 Supportive Analysis using Mixed-Effects Model for Repeated Measures (MMRM)

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,
- 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 Kenward-Rogers approximation will be used to estimate the denominator degrees of freedom when the covariance is unstructured.

Least squares means (LSMs) and their difference between each treatment group and the placebo will be estimated for Week 24, 48, 72, 96 and “overall” (the average of Week 24, 48, 72, and 96) for each of CDR-SB. The LSMs are interpreted as the expected CFB in the primary efficacy outcome. LSMs and standard errors (SEs) will be shown for each active treatment group and placebo. In addition, the percent slowing of decline expressed as the ratio of negative difference in LSMs over the LSM of placebo (i.e., [(–difference in LSM) / (LSM of placebo)] × 100%) will be displayed for each active treatment group. And its CI will be derived using the Delta method (refer to APPENDIX for more details on the derivation).

LSMs line plots over time will be displayed for the primary endpoint with separate lines for each treatment group.

Additionally, the same analysis described above will be repeated with the following groups in the model: AL002 15 mg/kg group, AL002 40 and 60 mg/kg combined group, and placebo group. All statistics described above from fitting the model will be reported only for the AL002 40 and 60 mg/kg combined group (or its comparison to placebo).

7.4.1.3 Analyses of Supportive Estimand for Primary Efficacy Endpoint

The analyses described in Sections 7.4.1.1 (pMMRM), and 7.4.1.2 (MMRM) will be repeated with the supportive estimand for the primary efficacy endpoint, as described in Section 6.2.1.3.

7.4.1.4 Sensitivity Analysis using Control-Based Pattern Mixture Model

To evaluate the impact of different patterns of missing CDR-SB values, a PMM with the primary estimand for the primary efficacy endpoint will be used in this study as a sensitivity analysis. PMMs have the advantages of allowing transparent and clinically interpretable formulations of the assumptions regarding unobserved data (Little & Rubin, 2019).

After the intermittent missing data are imputed, impute monotone missing at visits, up to the treatment period termination date (as defined in the protocol) plus 37 days, using a control-based PMM under the MNAR assumption. This is done because monotone missing data are presumed to be no longer on study drug, so could be treated as placebo control. Missing data will be imputed using sequential regression control-based pattern MI, where a separate regression model is estimated for imputation of each measurement at each visit.

The following sequential regression control-based pattern MI steps will be used:

i. With each call to PROC MI, only one time-point will be imputed. Each regression model will include explanatory variables: post-baseline measurement, APOE e4 status (e4 carrier, non-e4 carrier), all previous measurements at each time point (up to the missing value time-point). Range restrictions implied to imputed CDR-SB score: 0-18. Imputed data will consist of 100 imputed datasets.

ii. When imputing missing values for time-point *t*, the input dataset should include all placebo participants, but only those participants from AL002 that have values at time-point *t* missing (only those that need imputation at time-point *t*). Since participants from AL002 treatment groups with non-missing values at time-point *t* will not be included in the input dataset, they will not contribute to the estimation of an imputation model for time-point *t*. Imputation model will be estimated using placebo participants only. This way, missing values of participants from AL002 will be imputed based on the placebo participants' model.

iii. Repeat step ii for all other time-points sequentially. Participants whose missing values were imputed with the previous PROC MI call will be included in the input dataset for the next call to PROC MI. Thus, data for time-point *t*, filled in during the last call, will be used for predictor variables in the next call to PROC MI (for time-point $t + 1$).

iv. The multiple-imputed datasets of CDR-SB values will be used to compute the CFB in CDR-SB.

v. Perform the same primary analysis (pMMRM) with CFB in imputed or observed CDR-SB values and combine the results (mean differences and standard errors from multiple pMMRM) based on a standard MI methodology (Rubin 1987).

100 independent replications will be done with SAS PROC MI. The resulting 100 estimates of the treatment differences and standard errors will then be combined into the final estimate using SAS PROC MIANALYZE. Sample SAS codes for the MIs will be provided in a separate document. If changing seeds does not provide sufficient accuracy (two decimal places) for estimated standard errors, a larger number of replications will be used (i.e., start with 100, then maybe 200 or 500).

The control-based PMM analysis described above will be repeated with MMRM (Section 7.4.1.2), i.e., the pMMRM analysis will be replaced with MMRM in the step v.

7.4.1.5 Supplementary Analyses on Per-Protocol Analysis Set (PPS)

Supplementary analyses on PPS will be performed as follows (Table 7-21):

Table 7-21. Supplementary Analyses on PPS

Primary Efficacy Endpoint	Timing	Methodology
CFB to all scheduled post-baseline visits in CDR-SB score	Week 24, 48, 72, 96	pMMRM[a]
		MMRM[b]

pMMRM = proportional Mixed-Effects Model for Repeated Measures, MMRM = Mixed-Effects Model for Repeated Measures.

[a] same method as in Section 7.4.1.1

[b] same model as in Section 7.4.1.2

7.4.2 Analyses of Secondary Efficacy Endpoints

For the analysis of each of the secondary efficacy endpoints (Table 7-22), participants in the FAS who have a baseline value and at least one post-baseline value for the secondary endpoint being analyzed are included in the analysis.

Each of the secondary efficacy endpoints will be analyzed with pMMRM for proportional treatment effect (θ) as described for the primary efficacy endpoint (Section 7.4.1.1). The same variables except that the baseline CDR-SB score will be replaced with the baseline for the secondary endpoint being analyzed will be included in the model.

In addition, each of the secondary efficacy endpoints will be analyzed with MMRM for CFB across all scheduled post-baseline visits and CFB to each scheduled post-baseline visit as described for the primary efficacy endpoint (Section 7.4.1.2). The same variables except that the baseline CDR-SB score will be replaced with the baseline for the secondary endpoint being analyzed will be included in the model. Also, the same analyses using the supportive estimand as described for the primary efficacy endpoint (Section 7.4.1.3) will be repeated for each of the secondary efficacy endpoints.

A forest plot of proportional treatment effect and 95% CIs from pMMRM will be drawn by treatment group for all efficacy endpoints including the primary and secondary efficacy endpoints. In the same plot, the point estimates of the proportional treatment effect will be displayed. Similarly, the forest plot of LSM difference at Week 96 and 95% CIs from MMRM will be drawn by treatment group for all efficacy endpoints. In the same plot, the point estimates of the LSM difference at Week 96 and the percent slowing of decline will be displayed side by side. The same forest plot for the LSM difference at “overall” from MMRM will be provided.

All secondary efficacy endpoints will be analyzed without adjustment for multiplicity and presented with nominal p-values.

Table 7-22. Analyses of Secondary Efficacy Endpoints

Secondary Endpoints	Methodology [a]
CFB in MMSE to Week 24, 48, 72, 96	pMMRM [b], MMRM [c]
CFB in RBANS to Week 24, 48, 72, 96	pMMRM [b], MMRM [c]
CFB in ADAS-Cog13 to Week 24, 48, 72, 96	pMMRM [b], MMRM [c]
CFB in ADCS-ADL-MCI to Week 24, 48, 72, 96	pMMRM [b], MMRM [c]
CFB in ADCOMS to Week 24, 48, 72, 96	pMMRM [b], MMRM [c]
CFB in modified iADRS to Week 24, 48, 72, 96	pMMRM [b], MMRM [c]

pMMRM = proportional Mixed-Effects Model for Repeated Measures, MMRM = Mixed-Effects Model for Repeated Measures.

[a] For both primary and supportive estimands.

[b] same method as in Section 7.4.1.1

[c] same model as in Section 7.4.1.2

7.4.3 Subgroup Analyses

Subgroup analyses described in this section including figures will be performed for each of the efficacy endpoints, unless otherwise specified, for the subgroups in the FAS specified below:

- APOE e4 status
  - e4 Carrier
  - Non-e4 carrier
- AD diagnosis
  - Mild Cognitive Impairment (MCI) due to Alzheimer's disease
  - Mild Dementia due to Alzheimer's disease
- Age group
  - < 65 years
  - ≥ 65 – < 75 years
  - ≥ 75 years
- Sex
  - Female
  - Male

Subgroup analyses will be performed using the pMMRM model described in Section 7.4.1.1 by fitting the pMMRM model separately and respectively for each subgroup described above.

Subgroup analyses will also be performed using the MMRM model described in Section 7.4.1.2 by fitting the MMRM model separately and respectively for each subgroup described above.

If the pMMRM or MMRM model has convergence issue for a subgroup analysis, then only descriptive summaries will be provided for that subgroup.

Results will be reported for each subgroup separately and respectively.

LSMs line plots over time by treatment group will be displayed only for the primary efficacy endpoint and only for subgroups of APOE e4 status and AD diagnosis.

A forest plot of LSM difference at Week 96 and 90% CIs from MMRM will be drawn for all subgroups. In the same plot, the point estimates of the LSM difference at Week 96 and the proportional treatment effect from pMMRM will be displayed side by side.

7.5 Safety Analyses

Unless otherwise specified, all safety data will be summarized by treatment group, AL002 40 and 60 mg/kg combined group, and total AL002 group, primarily for the Non-e4/e4 Set. Some safety data may be summarized for the ATS.

Treatment period and analysis visit window definitions are described in Section 7.1.1.2.2.

In the case of multiple values in an analysis visit window and a single value may be required for each analysis visit window (e.g., CFB by visit usually requires a single value), data will be selected for analysis as described in Section 7.1.3.2, unless otherwise specified.

7.5.1 Extent of Exposure to Study Drug and Duration of Study

Extent of exposure to study drug (or duration of exposure of study drug) and duration of study will be summarized for both the ATS and the Non-e4/e4 Set.

Duration of exposure to study drug in days, weeks and months, participant-years of exposure, and treatment compliance (Section 6.3.1) will be summarized by treatment group, AL002 40 and 60 mg/kg combined group, total AL002 group, and overall.

Duration of exposure to study drug 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, and ≥ 96 weeks, where 1 week = 7 days.

Duration of study in days, weeks, and months will be summarized by treatment group, AL002 40 and 60 mg/kg combined group, total AL002 group, and overall.

Duration of study 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, and ≥ 96 weeks, where 1 week = 7 days.

The number of participants will also be mapped to one of the following categories: 12 months, 18 months and 24 months of dosing and of study.

The total number of doses of study drug and treatment compliance (%) will be summarized as a continuous measure. Treatment compliance (%) will also be categorized as < 80%, 80% – 120%, > 120%.

Duration of exposure to study drug and duration of study will be listed.

7.5.2 Adverse Events

AE related terms such as TEAE, SAE, and AESI are defined in Section 6.3.2. A 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.

Additionally, the following summary tables will be provided for the ATS:

- The summary of AEs as described above,
- TEAE by PT in descending order of total frequency,

- TEAE leading to early study drug discontinuation by PT in descending order of total frequency,
- Treatment-emergent SAE by PT 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,
- TEAE leading to death,
- Treatment-emergent AESI.

7.5.2.1 Adverse Events Counting Rules

At the participant level, the following AE counting rules apply:

- 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.

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.

7.5.2.2 Deaths

SAEs resulting in death regardless of whether it is treatment-emergent or not will be summarized by SOC and PT, and will be listed including any appropriate information where available.

7.5.3 Columbia Suicide Severity Rating Scale (C-SSRS)

For the C-SSRS, the number and percentage of participants with suicidal ideation, suicidal behavior, suicidal ideation or suicidal behavior, and non-suicidal self-injurious behavior as recorded on the C-SSRS scale, will be presented for each visit (refer to Table 7-2 for analysis visit window definition), 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 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 Study Day 1 will be included.

Only data recorded on the Since Last Visit version after Study Day 1 will be included in the treatment period.

A shift table from 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 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.

7.5.4 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.

7.5.4.1 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 Table 7-3 and Table 7-4 for analysis visit window definition); the actual values and CFB will be summarized.

In addition, laboratory data will be summarized with shift tables from baseline to each post-baseline visit and overall during the post-baseline period, which include all post-baseline data, by laboratory test, where applicable. Each participant's hematology, chemistry, urinalysis, and coagulation non-missing numeric values will be flagged as "low", "normal", or "high" relative to the normal ranges of the central laboratory, when applicable. Each participant's urinalysis non-missing categorical values will be flagged as "positive" (or "present") or "negative" (or "absent"), when applicable. For each post-baseline visit shift summary for a given laboratory test, participants who had at least one post-baseline value at that visit and a baseline value will be included. For overall, participants will be categorized according to the most severe post-baseline category for a given laboratory test.

Local laboratory data will not be summarized or listed.

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

7.5.4.2 Toxicity Grades for Laboratory Results

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. Toxicity grades for laboratory results will be summarized with shift tables from baseline to each post-baseline visit and overall during the treatment period by laboratory test, for laboratory parameters that had at least one Grade 1 or above result at baseline or any time post-baseline. For overall, participants will be categorized according to the most severe post-baseline toxicity grade for a given laboratory test. Participants with a toxicity grade ≥ 3 will be marked in the by-participant data listing.

7.5.4.3 Potential Serious Hepatotoxicity

The number and percentage of participants meeting the criteria of potential serious hepatotoxicity (Section 6.3.4.2) will be summarized and will be listed.

7.5.5 Electrocardiogram (ECG)

Actual results and CFB values for the average of triplicate 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 7-5 for analysis visit window definition) 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 and post-infusion) 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 7-23) 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 7-23. 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.

The same analyses described above will also be performed for the centrally read ECGs, when applicable.

7.5.6 Vital Signs

Vital signs data will be presented descriptively for each visit (refer to Table 7-7 and Table 7-8 for analysis visit window definition) and separated by predose and post-infusion (refer to Section 7.1.4.3 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 7-24 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 7-24. 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.

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

Incidence of the first occurrence of ARIA-E within each post-baseline visit will be summarized by radiographic severity for each visit (refer to Table 7-9 for analysis visit window definition) and overall during the treatment period. The same incidence table will be summarized for post-baseline new ARIA-H. In addition to radiographic severity for ARIA-H, individual radiographic severity for microhemorrhages, leptomeningeal hemosiderosis, and macrohemorrhages for the first occurrence of new ARIA-H will also be summarized by visit and overall during the treatment period.

Incidence of any occurrence of ARIA-E within each post-baseline visit will be summarized in the same fashion. 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 incidence table will be summarized for post-baseline new ARIA-H. In the case of multiple values in an analysis visit window, the same rules described above apply. In addition to radiographic severity for ARIA-H, individual radiographic severity for microhemorrhages, leptomeningeal hemosiderosis, and macrohemorrhages for the any occurrence of new ARIA-H will also be summarized by visit and overall during the treatment period. 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 new ARIA-H.

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

All the MRI summaries described above will also be provided separately for participants with the following APOE genotype(s) (1) e4/e4, (2) e4 carriers (including e2/e4, e3/e4 and e4/e4), (3) non-e4 carriers (excluding e2/e4, e3/e4 and e4/e4), and (4) e4 heterozygous carriers (including e2/e4 and e3/e4).

The Kaplan-Meier curve for the time to the first occurrence of ARIA-E will be plotted. For participants 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 and the last dose date plus 90 days. Similarly, the Kaplan-Meier curve for the time to the first occurrence of new ARIA-H will be plotted.

All MRI findings will be listed.

7.5.8 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 7-10 for analysis visit window definition), 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 worsens 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 worsening 3 categories.
  - Right eye best-corrected visual acuity worsens 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.

7.5.9 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 7-11 for analysis visit window definition) and overall during the treatment period. 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.

7.5.10 Physical Examinations (PE)

All PE findings will be listed.

7.5.11 Other Safety Assessments

7.5.11.1 Pregnancy Test

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

7.5.11.2 COVID-19

Impact of COVID-19 was collected for the following: participants impacted by COVID-19, participant dispositions impacted by COVID-19, AEs, assessments, significant protocol deviation related to COVID-19, cause of impact, study drug interruption caused by COVID-19. All the COVID-19 impacted events/participants will be displayed in the by-participant data listing.

7.6 Pharmacokinetic Endpoints

All PK summaries will be performed on the PK Set. AL002 concentration will be summarized by analysis visit (refer to Table 7-13 and Table 7-14 for analysis visit window definition) and nominal time point as collected, separately for serum and CSF PK. 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 hours, i.e., (time of collection – time of the first study drug administration + 1) and treatment group for the first dose, separately for serum and CSF PK. The same plot (linear and semi-log) will be repeated for the seventh dose.

AL002 mean (+ SD) trough concentration-time data will also be plotted (linear) by elapsed time since the first study drug administration (in nominal weeks) by ADA group (positive and negative), separately for serum and CSF PK. In each ADA group, all treatment groups will be combined. The ADA positive group includes all participants who had at least one positive ADA result any time post-baseline. The ADA negative group includes all participants whose ADA results were all negative post-baseline. Participants who did not have any ADA post-baseline result will be excluded from this plot.

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 analyses 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.

7.7 Exploratory PD Biomarker Endpoints

All PD biomarker analyses will be performed on the FAS. The key biomarker objectives are listed below:

- *PD assessment*: Assess the treatment effect in AL002 vs. placebo for the CFB in biomarker levels.
- *Correlation with CDR-SB*: Assess the treatment-related association between CFB in biomarker levels (fluid and imaging) and CFB in CDR-SB.
- *Baseline plasma pTau217 as disease staging variable*: Assess treatment effect in AL002 vs. placebo in CFB in COAs and plasma biomarkers with baseline plasma pTau217 as a disease staging variable.

Biomarkers will be bucketed into subset 1 and subset 2 based on the analysis scope, with more analyses planned for subset 1 compared to subset 2. Biomarker subsets are listed in Table 7-25. The analysis scopes are listed in Table 7-26, Table 7-27, and Table 7-28 for the key biomarker objectives.

Table 7-25. Biomarker Subsets

Biomarker Type	Subset 1	Subset 2
CSF	• sTREM2 (target engagement) • IL1RA (TREM2 engagement) • Osteopontin (TREM2 engagement) • pTau217 (amyloid and Tau) • MTBR Tau-243 (amyloid and Tau) • 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) • pTau181 (amyloid)
Plasma	• IL1RA (TREM2 engagement) • pTau217 (amyloid and Tau) • Aβ42/40 (amyloid) • GFAP (neuroinflammation and neurodegeneration) • NfL (neurodegeneration)	• pTau181 (amyloid)

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

Biomarker Type	Subset 1	Subset 2

Tau PET (normalized to cortical grey matter of cerebellum)	• Roll-up ROIs, SUVR measure:
	  ○ Medial temporal
	  ○ Temporal
	  ○ Frontal
	  ○ Cingulate
	  ○ Parietal
	  ○ Occipital
	  ○ Whole cortical gray matter
	  ○ Temporoparietal
	• Rowe metatemporal composite ROI, SUVR measure
	• Jack metatemporal composite ROI, SUVR measure	

MRI	• Volumetric parameters:
	  ○ Temporal cortex
	  ○ Parietal cortex
	  ○ Whole brain
	  ○ Hippocampus
	  ○ Ventricles	

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

Table 7-26. Analysis Scope for PD Assessment Objective

Analysis Scope	Endpoint	Analysis Method
Assess treatment effect of AL002 doses vs. placebo in the *FAS*	• CFB to scheduled post-baseline visits (see Section 7.7.1.1) in *plasma biomarker levels [subset 1 and subset 2]* • CFB to week 6, 48, 72 in *CSF biomarker levels [subset 1 and subset 2]* • CFB to week 48 in *amyloid PET [subset 1 and subset 2 parameters]* • CFB to week 48 and 72 in *Tau PET [subset 1 parameters] [a* and b*]* • CFB to scheduled post-baseline visits (see Section 7.7.1.1) in *MRI [subset 1 parameters]*	• MMRM (main estimand) [tables and figures] • pMMRM (main estimand) for only *subset 1 Tau PET parameters* [table] • Descriptive summaries (main estimand) [tables] • MMRM, pMMRM [table and figure] and descriptive summary [table] (supportive estimand) for subset 1 Tau PET parameters [b*] • MMRM [table and figure] and descriptive summary [table] (supportive estimand) for amyloid PET parameters • Listings

Analysis Scope	Endpoint	Analysis Method
Assess treatment effect of AL002 doses vs. placebo in *subgroups defined by* • Baseline demographics: *gender (male, female), age (< 65 years, ≥ 65 years), AD diagnosis (mild cognitive impairment (MCI), mild dementia (MD))* • APOE genotype: *e4 carrier, non-e4 carrier*	• CFB to scheduled post-baseline visits in *plasma biomarker levels*	• Descriptive summaries (main estimand) for subset 1 plasma biomarkers [tables] • MMRM (main estimand) ○ APOE e4 carrier and non-e4-carrier subgroups *[subset 1 only]* [tables and figures] ○ Baseline demographics subgroups *[subset 1 only]* (tables only)

CFB = change from baseline; CSF = cerebrospinal fluid; MMRM = Mixed-Effects Model for Repeated Measures; MRI = magnetic resonance imaging; PD = pharmacodynamic; PET = positron emission tomography.
a True baseline*: include participants with pre-dose Tau PET scan in the calculation for CFB.
b Redefined baseline*: include participants with either pre-dose Tau PET if evaluable or 1st post-dose evaluable Tau PET scan if pre-dose PET scan is missing in the calculation for CFB.

Table 7-27. Analysis Scope for Correlation with CDR-SB Objective

Analysis Scope	Endpoint	Analysis Method
Assess treatment-related association between CFB *in biomarker levels (plasma, CSF, amyloid PET and Tau PET) and CFB in CDR-SB in the FAS set*	• CFB to scheduled post-baseline visits (week 48, 72, 96) in CDR-SB and *subset 1 plasma biomarkers* • CFB to scheduled post-baseline visits (week 48, 72) in CDR-SB and *subset 1 CSF biomarkers* • CFB to week 48 in CDR-SB and *subset 1 amyloid PET parameters* • CFB to scheduled post-baseline visits (week 48, 72) in CDR-SB and *subset 1 Tau PET parameters (a* and b*)*	• Group-level scatterplots of adjusted mean difference from placebo in CDR-SB and *subset 1 biomarkers (plasma, CSF, amyloid PET and Tau PET)* with Pearson and Spearman correlations at matching timepoints (main estimand). • Adjusted correlative analyses [tables] of CFB in CDR-SB and *subset 1 biomarkers (plasma, CSF, amyloid PET and Tau PET)* at matching timepoints (main estimand)

CFB = change from baseline; CSF = cerebrospinal fluid; PET = positron emission tomography.
a True baseline*: include participants with pre-dose Tau PET scan in the calculation for CFB. *b* Redefined baseline*: include participants with either pre-dose Tau PET if evaluable or 1st post-dose evaluable Tau PET scan if pre-dose PET scan is missing in the calculation for CFB.

Table 7-28. Analysis Scope for Baseline plasma pTau217 as Disease Staging Variable Objective

Analysis Scope	Endpoint	Analysis Method
Assess treatment effect in AL002 vs. Placebo in COAs and subset 1 plasma biomarkers with baseline plasma pTau217 as disease staging variable	• CFB to scheduled post-baseline visits (week 24, 48, 72, 96) in COAs (CDR-SB, ADAS-Cog13, ADCS-ADL-MCI, ADCOMS, modified iADRS, MMSE, and RBANS) • CFB to scheduled post-baseline visits (week 24, 48, 72, 96) in *subset 1 plasma biomarkers*	• Subgroup analyses of CFB in COAs with subgroups based on baseline plasma pTau217 terciles (pMMRM, MMRM; main estimand) [tables and figures]. • Subgroup analyses of CFB in *subset 1 plasma biomarkers* with subgroups based on baseline plasma pTau217 terciles (MMRM; main estimand) [tables and figures].

COAs = clinical outcome assessments; CFB = change from baseline.

7.7.1 PD Assessment Objective

7.7.1.1 FAS

For exploratory PD biomarkers (CSF, plasma, amyloid PET, Tau PET and volumetric MRI) listed in Table 7-25 [subsets 1 and 2] in the FAS, their visit values, change from baseline (CFB) and percent change from baseline (PCFB) for the main estimand will be summarized by treatment group over time (all visits) using descriptive statistics (Table 7-26).

Comparisons of CFB between AL002 dose groups vs. placebo will be explored for the main estimand using MMRM models (see Section 7.4.1.2) with treatment group, categorical visit, visit-by-treatment interaction, baseline biomarker, and APOE e4 status of e4 carrier vs. non-e4 carrier as fixed effects (Table 7-26). Treatment comparisons will be reported for specified visits as indicated below:

- Plasma biomarkers:
  - AD-pathology (Aβ42/40, pTau217, MTBR-Tau243): week 12, 24, 48, 72 and 96
  - AD-pathology (pTau181): 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 and 72
- Amyloid PET parameters: week 48
- Tau PET parameters: week 48 and 72
- Volumetric MRI parameters: week 48, 72 and 96

Additionally, the same analysis for the main estimand described above will be repeated with the following groups in the model: AL002 15 mg/kg group, AL002 40 and 60 mg/kg combined group, and placebo group. All statistics described above from fitting the MMRM model will be reported only for the AL002 40 and 60 mg/kg combined group (or its comparison to placebo).

For Tau PET parameters [subset 1] in Table 7-25, a sensitivity analysis (main estimand) will be conducted with similar descriptive summaries and MMRM models for the subset with redefined baseline (either pre-dose Tau PET if evaluable or the first post-dose evaluable Tau PET scan if pre-dose PET scan

is missing) (Table 7-26). A pMMRM model (main estimand) will be additionally conducted for both subsets of true baseline and redefined baseline (Table 7-26).

Given the limited sample size mapped to the Week 96 analysis visit for CSF, Amyloid PET and Tau PET, this visit will only be summarized descriptively and excluded from modelling (i.e., pMMRM and MMRM).

For amyloid PET centiloids measure, the number of participants with amyloid clearance (positive [centiloids ≥ 24.1] at baseline and negative [centiloids < 24.1] at week 48), and percentage with 95% CI (mid-p method), will be summarized by treatment group. Treatment comparison (vs. placebo) will be based on mid-p method.

Additional analyses based on supportive estimand will be provided for Tau PET ROIs [subset 1] for the subset with redefined baseline (descriptive summary, MMRM and pMMRM), and amyloid PET ROIs (descriptive summary and MMRM) [Table 7-25].

7.7.1.2 Subgroups

Descriptive summaries and MMRM models will be provided for subset 1 plasma biomarkers for subgroups of APOE e4 status (e4 carrier, non-e4 carrier), gender (male, female), age group (< 65 years, ≥ 65 years), AD diagnosis (mild cognitive impairment, mild dementia) (Table 7-25) in the FAS. Listings for the main estimand will be provided for plasma and CSF biomarkers [subsets 1 and 2], volumetric MRI parameters [subset 1], amyloid PET parameters [subsets 1 and 2], and Tau PET parameters [subset 1] (Table 7-26).

7.7.2 Correlation with CDR-SB Objective

Treatment-related association between CFB in biomarker levels (CSF, plasma, amyloid PET and Tau PET) [subset 1] in Table 7-25 and CFB in CDR-SB will be assessed. Specifically, the following analyses will be conducted for the main estimand [Table 7-27].

- Adjusted correlative analyses of CFB in CDR-SB and CFB in specified subset 1 biomarkers. Three MMRM models will be assessed.
    - Model 1 of CFB in biomarker with treatment group, categorical visit, visit-by-treatment interaction, baseline biomarker, and APOE e4 status as fixed effects.
    - Model 2 of CFB in CDR-SB with the same fixed effects terms as in model 1, and baseline CDR-SB as additional fixed effects term.
    - Model 3 of CFB in CDR-SB with the same fixed effects terms as in model 1, and baseline CDR-SB and CFB in biomarker as additional fixed effects terms.
    - The three models include only participants with both CFB in CDR-SB and CFB in biomarker at matching timepoints.
    - Similar analyses will be repeated with the following treatment groups in the model: AL002 15 mg/kg group, AL002 40 and 60 mg/kg combined group, and placebo group. Statistics from fitting the MMRM model will be reported only for the AL002 40 and 60 mg/kg combined group (or its comparison to placebo).
- Group-level scatterplots of adjusted mean difference from placebo in CDR-SB and adjusted mean difference from placebo in specified subset 1 biomarkers at matching timepoints.
    - The adjusted mean difference from placebo is the least squares mean difference (vs. placebo) in the corresponding MMRM analyses.

- Add the error bars (±SE) for adjusted mean difference from placebo in CDR-SB.
- Include AL002 40 and 60 mg/kg combined group in the scatterplot.
- Add Pearson and Spearman correlation coefficients, and linear regression line (exclude the combined group AL002 40 and 60 mg/kg).

For subset 1 Tau PET parameters in Table 7-25, a sensitivity analysis will be additionally conducted with similar analyses for the subset with redefined baseline.

7.7.3 Baseline Plasma pTau217 as Disease Staging Variable Objective

Subgroup analyses of CFB in COAs (primary and secondary endpoints) with subgroups based on baseline plasma pTau217 terciles will be conducted similarly as described in Section 7.4.1.2 using pMMRM and MMRM models for the main estimand [Table 7-25]. Baseline plasma pTau217 tercile subgroups are defined as below:

- Low expression (levels $\leq 1^{st}$ tercile cutpoint)
- Medium expression (1^{st} tercile cutpoint < levels $\leq 2^{nd}$ tercile cutpoint)
- High expression (levels > 2^{nd} tercile cutpoint)

Subgroup analyses of CFB in subset 1 plasma biomarkers subgroups based on baseline plasma pTau217 terciles will be conducted using MMRM for the main estimand [Table 7-28].

7.7.4 Miscellaneous

Demographics and baseline characteristics will be summarized by treatment group, AL002 40 and 60 mg/kg combined group, total AL002 group, and overall for FAS subsets of participants with amyloid PET data, Tau PET data (at least one evaluable baseline or post-baseline PET scan), and CSF data (at least one evaluable baseline or post-baseline CSF measurement for the subset 1 CSF biomarkers) to assess the representativeness of these subsets to the FAS.

A listing will be provided for the amyloid probability score (APS), derived from the PrecivityAD™ algorithm that combines Aβ42/40, APOE genotype and age, for the randomized participants with test results.

7.8 Immunogenicity Endpoints

The exploratory analyses for immunogenicity endpoints will be performed on all randomized participants who received at least one dose of study drug and 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 (refer to Table 7-12 for analysis visit window definition) and treatment group. The titer numerical results will be summarized with median, minimum, and maximum by visit and treatment group.

Shift from baseline in blood serum classes will be summarized by visit (refer to Table 7-12 for analysis visit window definition) and treatment group using the frequency count and percentage of participants in each category.

A listing of ADAs will be provided.

7.9 Summaries for APOE e4-Homozygous Participants Set (e4/e4 Set)

In addition to the participant disposition specified in Section 7.2.1 and MRI findings specified in Section 7.5.7, the demographics and baseline characteristics specified in Section 7.3.1 and the summary of AEs and TEAE by SOC, PT and severity specified in Section 7.5.2 will be summarized using descriptive statistics for the e4/e4 Set (Section 5.4). In addition, swim lane plots of ARIA-E and ARIA-H events over time since the first study drug administration (in days) will be provided for the e4/e4 Set. All by-participant data listings will be provided for the ARS (unless otherwise specified) which already include the e4/e4 participants. So, no separate listings will be provided for the subset.

8. ANALYSES PERFORMED BEFORE DATABASE CLOSURE

The database lock will occur when all participants either completed or prematurely discontinued the planned study treatment period of this study. No efficacy interim analyses will be conducted prior to the database lock of the study.

9. CHANGES FROM METHODS PLANNED IN THE PROTOCOL

The statement of the primary estimand given in Section 6.2.1.2 clarified that the target population excludes e4/e4 participants, that the primary estimand specified in the latest version of the protocol did not specify this exclusion. This clarification does not result in any differences for summaries or analyses.

The criteria for PPS in Section 5.3.2 are updated as the one specified in the protocol was too general and did not meet the needs of PPS.

The summary of physical examinations will not be performed, since clinically significant physical examination changes will be captured in the AE summaries.

The supportive analysis using LME model is removed from this SAP. The primary analysis using the pMMRM model is based on the assumption of proportionality, which is an inherit assumption of the LME model. If the assumption of proportionality is not met under the pMMRM model, the results of analysis using the MMRM model will be used to interpret the study. For this reason, the supportive analysis using LME model has been removed from SAP.

Safety analyses will primarily be performed for the Non-e4/e4 Set, instead of the Safety Set as specified in the protocol, because of the removal of the e4/e4 participants from the participant population being studied. The AL002-2 study originally included enrollment of participants who were APOE e4 homozygotes (e4/e4). However, further enrollment of participants with this APOE genotype was permanently stopped after the evaluation of safety among the early enrolled participants with e4/e4. Therefore, the primary objective of the study changed to the assessment of AL002 in the participants without e4/e4.

The exploratory analyses of WLSA data (optional study) and genetics will be excluded from the SAP.

10. STATISTICAL SOFTWARE

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

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12. APPENDIX

Delta method:

Let X and Y be two random variables with means μ_X and μ_Y, respectively; and let $R\ (\mu_X, \mu_Y) = \frac{\mu_X}{\mu_Y}$ be the ratio. Then

$$\frac{\partial y}{\partial \mu_X} R\ (\mu_X, \mu_Y) = \frac{1}{\mu_Y}$$

$$\frac{\partial y}{\partial \mu_Y} R\ (\mu_X, \mu_Y) = -\frac{\mu_X}{\mu_Y^2}$$

$$\boldsymbol{E\left(\frac{X}{Y}\right) \approx \frac{\mu_X}{\mu_Y}} \qquad \textbf{(1)}$$

$$Var\left(\frac{X}{Y}\right) \approx \frac{1}{\mu_Y^2} VarX + \frac{\mu_X^2}{\mu_Y^4} VarY - 2\frac{\mu_X}{\mu_Y^3} Cov(X,Y)$$

When X and Y are independent (e.g., in two independent treatment arms),

$$\boldsymbol{Var\left(\frac{X}{Y}\right) \approx \frac{1}{\mu_Y^2} VarX + \frac{\mu_X^2}{\mu_Y^4} VarY} \qquad \textbf{(2)}$$

Percent slowing of decline estimation based on MMRM

When applying the Delta method to the MMRM outputs, μ_X and μ_Y will be substituted by the estimated LSMs of the CFB at the end-of-study visit (time = 4 in the specific example below), and their variances will be the estimated variances. The table below presents the related parameter estimates that can be used for the percent slowing of decline estimation. Substituting these related estimates into formula (1) and formula (2) will yield the percent slowing of decline estimation and the corresponding p-values.

Group	Time	Estimate	Standard Error
P	4	$\mu_Y = 4.5489$	$\sqrt{VarY} = 0.6143$
T	4	$\mu_X = 3.0991$	$\sqrt{VarX} = 0.5903$

13. VERSION HISTORY

Version	Date	Summary of Changes	Reason for Change
1.0	31OCT2020	NA	NA
2.0	16MAY2024	SAP was rewritten.	Switch to Everest SAP template. Follow multiple protocol amendments.
		All analyses will primarily be performed for the Non-e4/e4 Set.	To align with the change in target population (see Section 5.3).
		Added the Modified iADRS endpoint and associated analyses.	The modified iADRS is a composite tool combining scores from the ADAS-Cog13 and the ADCS-MCI-ADL that provides an evaluation of clinical disease progression.
		Changed primary efficacy analysis method from Bayesian ordinal longitudinal disease progression model (DPM) to pMMRM.	DPM is deemed not well control family-wise type 1 error.
		Added sensitivity analysis using PMM.	To evaluate the impact of different patterns of missing CDR-SB values.
		Excluded those participants who received <3 doses of study drug in PPS definition.	To provide more specific requirements on dosing as part of the PPS definition.
		Added ARIA endpoints and associated analyses.	To summarize ARIA abnormalities based on MRI data.
		Added PCS criteria for safety endpoints.	To summarize safety abnormalities.
		Removed Plasma sTREM2 endpoint.	Plasma sTREM2 will not be used for decision-making due to technical interference by AL002 with the analyte.
		Added Tau PET and amyloid PET endpoints in Table 7-25.	Tau PET and amyloid PET analyses will be included in the CSR.
		Removed correlation analyses of PD biomarkers with safety, PK, immunogenicity, other PD biomarkers.	These correlation analyses are exploratory and excluded from the CSR.