STATISTICAL ANALYSIS PLAN FOR PART 2

Protocol Number:	INFRONT-3 (AL001-3)
Protocol Title:	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AL001 in Individuals at Risk For or With Frontotemporal Dementia Due to Heterozygous Mutations in the Progranulin Gene
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Indication:	Frontotemporal dementia (FTD)
Dosage Form/Strength:	IV 60 mg/kg
Study Phase:	3
Regulatory Agency Identifier(s):	IND Number: [redacted] EU Clinical Trial Number: 2023-506873-36

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Sponsor: Alector Inc.
131 Oyster Point Boulevard, Suite 600
South San Francisco, CA 94080, US
Telephone: +1 650-837-0384

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SAP APPROVAL

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AL001 in Individuals at Risk For or With Frontotemporal Dementia Due to Heterozygous Mutations in the Progranulin Gene
I approve the Statistical Analysis Plan, dated 30 Sep 2025.

Authored by: Grace Chao, MS [redacted]

Refer to the signature manifest at the end of the document.

Signature | Date (dd-Mmm-yyyy)

Approved by: Arthur Mavorga, PhD [redacted]

Refer to the signature manifest at the end of the document.

Signature | Date (dd-Mmm-yyyy)

Approved by: Jinglin Zhong, PhD [redacted]

Refer to the signature manifest at the end of the document.

Signature | Date (dd-Mmm-yyyy)

SAP VERSION HISTORY

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)	Brief Description of Change(s) and Rationale
1.0	30 Sep 2025	Version 6.0, 07 Sep 2023	Original document creation.

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LIST OF ABBREVIATIONS

Abbreviation	Description
ADA	antidrug antibody
AE	adverse event
ALLFTD	FTD research consortium consisting of Advancing Research and Treatment in Frontotemporal Lobar Degeneration (ARTFL) and Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS)
ATC	Anatomical therapeutic chemical
BMI	body mass index
bvFTD	Behavioral variant frontotemporal dementia
CDR plus NACC FTLD	Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Disease Coordinating Center frontotemporal lobar degeneration Behavior and Language domains
CDR plus NACC FTLD-GS	Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Disease Coordinating Center frontotemporal lobar degeneration Behavior and Language domains - global score
CDR plus NACC FTLD-SB	Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Disease Coordinating Center frontotemporal lobar degeneration Behavior and Language domains - sum of boxes
CFB	change from baseline
CGI-I	clinical global impression - improvement
CGI-S	clinical global impression - severity
CI	confidence interval
COA	clinical outcome assessment
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
CSR	clinical study report
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EQ-5D	EuroQOL-5 Dimensions, 5 levels
EuroQol	European Quality of Life
FAS	Full analysis set
FRS	Frontotemporal dementia rating scale
FTD	Frontotemporal dementia

Abbreviation	Description
FTLD	Frontotemporal lobar dementia
GFAP	Glial fibrillary acidic protein
GRN	Progranulin gene
IV	intravenous(ly)
LLOQ	lower limit of quantitation
LP	lumbar puncture
LSMean	least squares means
Max	Maximum
MedDRA	medical dictionary for regulatory activities
Min	Minimum
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
msec	Millisecond
NE	neurological examination
NfL	Neurofilament light-chain
OLE	open-label extension
PCFB	percentage change from baseline
PD	Pharmacodynamic
PE	physical examination
PGRN	Progranulin protein
PK	Pharmacokinetic
PT	preferred term
Q1	25th quartile
Q3	75th quartile
q4w	every 4 weeks
QTcF	QT interval corrected using the Fridericia formula (QTcF = QT/(RR)1/3)
RBANS	repeatable battery for the assessment of neuropsychological status
RoI	Region of Interest
RUD-Lite	Resource utilization in dementia – lite version
SAE	serious adverse event
SAF	Safety set

Abbreviation	Description
SAP	statistical analysis plan
SAS®	Statistical Analysis Software, SAS Institute
SD	standard deviation
SE	standard error
SOC	system organ class
Sheehan-STS	Sheehan-suicidality tracking scale
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantitation
VAS	visual analogue scale
WHO DD	World Health Organization Drug Dictionary
WLSA	Winterlight Labs speech assessment
ZBI	Zarit burden interview

1. INTRODUCTION

Study INFRONT-3 is a Phase 3 study designed to evaluate the efficacy and safety of AL001 (latozinemab) compared to placebo in individuals with frontotemporal dementia (FTD) due to a heterozygous granulin gene (GRN) mutation. The study is conducted in 2 parts. Part 1 is a 96-week randomized, double-blind placebo-controlled treatment period. Part 2 is an optional 96-week open-label extension (OLE) for eligible participants who have completed Part 1. All participants in the OLE, whether they received latozinemab or placebo in Part 1, will receive open-label latozinemab.

There are 2 separate statistical analysis plans (SAP) for Part 1 and Part 2 data, respectively. The clinical data cutoff date (CCoD) for the Part 1 SAP is when all participants have either completed Visit 25/Week 96 or have prematurely discontinued the planned study treatment period of Part 1 of this study.

The purpose of this SAP is to provide general guidelines for the analysis of data collected from Part 2 of the INFRONT-3 study. Additionally, this SAP includes the analysis of data from both Part 1 and Part 2 for selected clinical outcome assessment (COA) and biomarker endpoints. The inclusion of Part 1 and Part 2 data is outlined in Appendix 1 and detailed in each analysis section. The SAP contains detailed technical elaborations of the principal features of the analysis described in the protocol and includes detailed procedures for executing the statistical analyses. 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. Detailed table, figure and listing (TFL) specifications will be provided in a separate document, and additional technical details will be outlined in a technical specifications document, and both will be finalized prior to execution of the analyses outlined in this SAP.

At the time of Part 1 database lock, all efficacy and safety data and PK/Biomarker data collected in Part 1 (including the Part 1 safety follow-up visit) are described and analyzed according to Part 1 SAP, which constitutes the final CSR analysis for Part 1 of this study. Analysis of Part 2 data up to Part 1 CCoD will be described and analyzed according to Part 2 SAP and submitted for health authority review in the initial marketing application submissions.

A final analysis of Part 2 will be conducted according to this SAP when all participants have completed the study and data base is locked for the entire study.

1.1. Study Objectives and Endpoints

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the long-term safety and tolerability of latozinemab in participants who have completed Part 1 of the study	• Incidence, nature, and severity of AEs and SAEs • Physical examination abnormalities • Neurological examination abnormalities • Changes in vital signs from baseline over time • Changes in electrocardiograms from baseline over time • MRI abnormalities • Changes in clinical laboratory tests from baseline over time • Sheehan-suicidality Tracking Scale (Sheehan-STS) • Incidence of ADAs to latozinemab
Exploratory Endpoints	
COAs, biomarkers and other efficacy assessments conducted during the OLE are considered exploratory. The exploratory objectives of the OLE period of the study are to assess the long-term effect of latozinemab in participants who have completed Part 1 of the study on the following:	
• PD and disease pathology biomarkers	• PGRN concentrations in plasma and optional CSF • NfL concentrations in serum and optional CSF • Glial fibrillary acidic protein (GFAP) concentrations in plasma and optional CSF • Structural volumetric MRI regional brain volume; arterial spin labeling, diffusion-tensor imaging, and other MRI measures
• Clinical progression as measured by COAs	The overall change from baseline on the scores of the instruments in the COAs • CDR® plus NACC FTLD • CGI-I • CGI-S • RBANS • FRS • WLA, for participants who agree to participate in these optional assessments only
• Quality of Life COAs	• EQ-5D score • ZBI score
• Pharmacoeconomic COA	• Resource Utilization in Dementia-Lite (RUD-Lite) score
• Exposure-response relationships	Exposure-response relationships for relevant biomarkers (eg, PGRN, NfL), efficacy responses in relation to latozinemab exposure

1.2. Study Design

The study has 2 parts: A double-blind, placebo-controlled treatment period (Part 1), followed by an optional OLE period (Part 2).

1.2.1. Part 1: Double-blind, Placebo-controlled Treatment Period

Part 1 is a 96-week randomized, double-blind, placebo-controlled treatment period to evaluate the efficacy and safety of latozinemab 60 mg/kg, q4w compared to placebo in participants who are known carriers of a heterozygous loss-of-function GRN mutation causative of FTD. Participants are randomized to receive latozinemab or placebo in a 3:2 ratio, respectively.

1.2.2. Part 2: Optional Open-label Extension

If a Part 1 participant completes 96 weeks of treatment, they are eligible to be rolled over into the optional Part 2 portion of the study. Part 1 participants may be excluded from continuing in Part 2 if in the opinion of the investigator, continued treatment with latozinemab at the conclusion of Part 1 is not beneficial or safe for the participant. Part 1 participants who have been admitted to a nursing home/assisted living facility are not eligible for participation in Part 2. All participants in Part 2, whether they received latozinemab or placebo in Part 1, will receive open-label latozinemab at a dose of 60 mg/kg, q4w, for up to 25 doses over a 96-week dosing period.

Treatment assignment in Part 1 (latozinemab or placebo) will remain blinded to investigators, participants and raters until Part 2 is completed and the Part 2 data for all participants have been cleaned and locked.

A Schedule of Assessments can be referred to in the protocol.

2. STATISTICAL HYPOTHESES AND MULTIPLICITY ADJUSTMENT

Part 2 of the study is to characterize the long-term safety and tolerability of latozinemab, no formal statistical hypotheses tests will be defined or tested; as a result, no multiplicity adjustments are required.

2.1. Definition of Analysis Sets

The following analysis sets are defined in Table 2.

Table 2: Analysis Sets

Analysis Set	Definition
Full analysis set (FAS)	The subset of the participants who were randomized to study treatment arm in Part 1, received any amount of study drug, including both those who progressed to Part 2 and those who did not. Participants in this group will be analyzed according to their randomized treatment group in Part 1 (Placebo-Latozinemab and Latozinemab-Latozinemab).
FAS-symptomatic	The subset of the FAS who were symptomatic at Part 1 baseline.
All Part 2 enrolled participants (ENR-Part2)	All participants who signed Part 2 informed consent form.
Safety analysis set in Part 2 (SAF-Part2)	The subset of the ENR-Part2 who have received any amount of study drug in Part 2. Participants in this set will be analyzed according to their actual treatment group in Part 1 (Placebo-Latozinemab and Latozinemab-Latozinemab).
SAF-Part2-symptomatic	This is the subset of the SAF-Part2 which includes participants who were symptomatic at Part 1 baseline.
SAF-Part2-at risk	This is the subset of the SAF-Part2 which includes participants who were at risk (pre-symptomatic) at Part 1 baseline.
Full analysis set in Part 2 (FAS-Part2)	The subset of the ENR-Part2 who have received any amount of study drug in Part 2. Participants in this group will be analyzed according to their randomized treatment group in Part 1(Placebo-Latozinemab and Latozinemab-Latozinemab).
Full analysis set in Part 2-symptomatic (FAS-Part2-symtomatic)	This is the subset of the FAS-Part2 which includes participants who were symptomatic at Part 1 baseline.
Full analysis set in Part 2-at risk (FAS-Part2-at risk)	This is the subset of the FAS-Part2 which includes participants who were at risk (pre-symptomatic) at Part 1 baseline.
Pharmacokinetic set in Part 2 (PK-Part2)	The subset of participants in SAF-Part2 who had at least one post-baseline measurable assessment in Part 2 for determination of PK concentration.

3. STATISTICAL ANALYSIS

3.1. General Considerations

OLE and Part 2 are used interchangeably in the protocol and will be referred to as Part 2 in this document.

Unless specified otherwise, TFLs will be presented by treatment group, visit and timepoint (ie, pre-dose and post-dose), as applicable.

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.

Specifications of each table, listing and figure will be documented in a separate programming document, which may include technical definitions or sample code snippets.

All analyses will be conducted using SAS Version 9.4 or later. If necessary, additional analysis conducted in other software will be documented in the CSR.

3.1.1. Definitions, Derivations and Classifications

Definition of Part 2 Day 1

In addition to Day 1 defined in Part 1 SAP (also referred as Part 1 Day 1 throughout the SAP), a separate Part 2 Day 1 will be derived, defined as the first day of study treatment in Part 2 (Visit 26/Week 100).

Definition of Part 2 Baseline

In addition to the baseline defined in Part 1 SAP (also referred to as Part 1 baseline throughout the SAP), a separate Part 2 baseline will be derived, defined as the last available non-missing value between analysis visit window of Week 96 (or the nominal visit at Week 96 if no analysis visit window is applied for that measurement) and prior to study drug administration on Part 2 Day 1. For coagulation, the baseline will use analysis visit window of Week 92 instead of Week 96. Unless specified otherwise, assessments taken on the same day as Part 2 Day 1 will be assumed to be before the treatment (pre-dose) unless indicated to be obtained after the treatment (post-dose).

The baseline value for any measures planned to be taken with replicates at the same timepoint (eg, triplicate electrocardiogram parameters) will be the average of those replicate measurements using the same definition of baseline above.

Definition of Part 2 Study Day

In addition to the study day defined in Part 1 SAP (also referred as Part 1 study day throughout the SAP), a separate Part 2 study day will be computed as follows.

- Part 2 Study Day = (Date of event - Date of first dose of study treatment in Part 2) + 1 if the date of the event is on or after the date of the first study treatment in Part 2.
- Part 2 Study Day = (Date of event - Date of first dose of study treatment in Part 2) if the date of the event is prior to the date of the first study treatment in Part 2.

Derivations Involving Dates

Please refer to Part 1 SAP.

3.1.2. Windowing, Unscheduled Visits and Repeat Test Results

The general principle used for efficacy, safety and biomarker analyses is that visits will be allocated into analysis visit windows for purposes of summarization. These window definitions and analysis value selection rules (ie, in the case of multiple visits within the same analysis window) will be described in a separate document.

3.1.3. Handling of Values Above or Below Limits of Quantification

Please refer to Part 1 SAP.

3.1.4. Handling of Missing Data or Dropouts

Unless otherwise specified, missing data will not be imputed, in general (eg, laboratory values).

3.1.4.1. Handling of Missing Data in Concomitant Medication and Adverse Event

Please refer to Part 1 SAP.

3.2. Participant Disposition and Protocol Deviations

3.2.1. Participant Disposition

Participant disposition for Part 2 will be described for all Part 2 enrolled participants , including the number of participants enrolled into Part 2, treated, the number and percentage of participants who completed the study treatment, or discontinued study treatment early (and reasons for study treatment discontinuation), the number and percentage of participants who completed the study, or discontinued early (and reasons for study discontinuation).

Kaplan-Meier curves for time to study treatment discontinuation will be provided for each treatment group, similar to those described in Part 1 SAP, incorporating data from both Part 1 and Part 2, for the FAS.

3.2.2. Protocol Deviations

The number and percentage of participants with significant protocol deviations in Part 2 will be tabulated for each deviation category and by groups, for the SAF-Part2.

3.3. Participant Characteristics

3.3.1. Demographic and Other Baseline Characteristics

Descriptive summaries for demographics, baseline COAs, and baseline biomarkers similar to those described in Part 1 SAP will be provided by groups and by Part 1 baseline symptomatic status, for the SAF-Part2.

The following Part 2 baselines will be applied to those summaries.

- Weight, height and BMI
- COAs
- Biomarker (fluid and imaging) values

Age is not re-collected on the eCRF at Part 2, therefore the age at screening plus 2 years will be used for Part 2 summary of demographics. Other demographic information (eg, sex, race) and height will remain the same as in Part 1.

Baseline disease characteristics will be summarized by groups, using the SAF-Part2-symptomatic. Part 2 baseline disease characteristics are defined as the last available assessment prior to treatment on Part 2 Day 1, screening visit will be excluded from Part 2 baseline characteristics derivation.

3.3.2. Medical History

There is no additional data collected for Part 2; therefore, no additional medical history summaries or listings will be provided.

3.3.3. Concomitant Medical and Surgical Treatment Procedures

A concomitant medical or surgical treatment procedure in Part 2 is any therapeutic and diagnostic intervention or diagnosis assessment performed between the dates of the first dose of study drug in Part 2 and Part 2 End of Study.

The number and percentages of all concomitant medical and surgical treatment procedures in Part 2 will be summarized by groups using the SAF-Part2.

3.3.4. Concomitant Medications

A medication will be considered "concomitant" in Part 2 if the end date of administration is after the start of study treatment administration in Part 2 or if the start date is at or after the start of study treatment administration in Part 2. Details on handling of partial dates are specified in a separate technical document.

The number and percentage of all concomitant medications in Part 2 will be summarized by ATC level 3 and PT, by groups, using the SAF-Part2.

3.3.5. Extent of Exposure to Study Drug and Duration of Study

Similar analyses to those described in Part 1 SAP will be performed for the data in Part 2. The summary tables will be provided for the SAF-Part2, by groups, and by Part 1 baseline symptomatic status.

3.3.5.1. Extent of Exposure to Study Drug

Duration of exposure (days) will be calculated as the minimum of:

- If the participant did not die:
  - Minimum of (the date of last dose of study treatment during Part 2 - date of first dose in Part 2+ 28 days dosing interval, CCoD - date of first dose in Part 2+1 day)
- If the participant did die in Part 2: date of death - date of first dose in Part 2+ 1 day

A categorical summary of duration of exposure will be provided in the following intervals:

- <24 weeks
- ≥24 to <48 weeks
- ≥48 to <72 weeks
- ≥72 to <96 weeks
- ≥96 weeks

3.3.5.2. Study Duration

Study duration will be calculated as:

- Duration (days) = study completion date in Part 2 - first date of study drug in Part 2 + 1 day

A categorical summary of the duration of study in weeks will be provided in the following intervals:

- <24 weeks
- ≥24 to <48 weeks
- ≥48 to <72 weeks
- ≥72 to <96 weeks
- ≥96 weeks

3.3.5.3. Treatment Compliance

The number of infusions of study drug is defined as the total number of infusions a participant received, as recorded in the eCRF. The total number of infusions received and expected of study drug will be summarized as a continuous measure.

Treatment compliance is defined as the number of infusions received divided by the number of infusions expected. Treatment compliance is calculated across all planned doses during Part 2, up to the date of withdrawal, if participants discontinued from study drug early.

Treatment compliance (%) will be summarized in the following categories: <80%, ≥80 - <120%, and ≥120%.

3.4. Primary Analyses (Safety Analyses)

The default analysis set for safety is the SAF-Part2 (ie, regardless of symptomatic or at-risk status), unless otherwise specified.

For the change from baseline (CFB) analysis of safety summaries, the Part 2 baseline will be used.

3.4.1. Adverse Events

Similar analyses to those described in Part 1 SAP will be performed, for the data in Part 2. In addition to the AE summaries on SAF-Part2, selected AE tables on SAF-Part2-symptomatic will

be provided, Table 3 describes which summaries of TEAEs will be produced by each analysis set.

Treatment-emergent AE (TEAE) in Part 2 will be defined as those events that first occurred after treatment initiation in Part 2, and on or before the earliest of +28 days after the last treatment received in Part 2, or the date of death, or the CCoD.

For the purpose of inclusion in TEAE summaries, incomplete AE onset and end dates will be imputed using the rules outlined in a separate technical document.

Table 3: Summary of Treatment-emergent Adverse Event Tables by Analysis Set

TEAE Summary Table	Analysis Set(s)
All TEAEs:	
• TEAEs by SOC and PT	1,2
• TEAEs by PT in decreasing frequency	1
• TEAEs by SOC, PT and maximum severity	1
All Treatment-related TEAEs:	
• Treatment-related TEAEs by SOC and PT	1,2
• Treatment-related TEAEs by PT in decreasing frequency	1
• Treatment-related TEAEs by SOC, PT and maximum severity	1
All TEAEs Leading to Study Treatment Discontinuation or Interruption:	
• TEAE leading to treatment discontinuation by SOC and PT	1,2
• TEAE leading to treatment discontinuation by PT in decreasing frequency	1
All TESAEs:	
• TESAEs by SOC and PT	1,2
• TESAEs by PT in decreasing frequency	1
All Treatment-related TESAEs:	
• TESAEs by SOC and PT	1,2
• TESAEs by PT in decreasing frequency	1
All TEAE Leading to Death:	
• TEAE leading to death by SOC and PT	1

1=SAF-Part2; 2=SAF-Part2-symptomatic.

3.4.2. Sheehan-Suicidality Tracking Scale (Sheehan-STS)

Sheehan-STS total score will be summarized descriptively at each visit in Part 2 and by treatment group.

In addition, the Sheehan-STS will be mapped to the 2010 Columbia Classification Algorithm of Suicide Assessment (C-CASA) (see details in Part 1 SAP). The C-CASA scale is intended to aid in clinical interpretation of suicidal ideation and behavior. Categorical results of the C-CASA will be summarized by visit and by worst post-baseline visit for each treatment group in Part 2.

3.4.3. Laboratory Data

Clinical laboratory data to be summarized includes hematology, clinical chemistry, coagulation, and urinalysis data in Part 2. Handling of non-numeric qualifiers for below or above limits of quantitation are outlined in Part 1 SAP.

Central laboratory test results (actual values and CFB) will be summarized with descriptive statistics by parameter for each post-baseline visit by treatment group.

Shift tables will be used to summarize the CFB to worst post-baseline value with counts and percentages for hematology and serum chemistry.

For selected laboratory parameters, potentially clinically significant (PCS) categories are defined in Part 1 SAP. The number and percentage of subjects with post-baseline PCS for each PCS category will be summarized by visit and overall post-baseline visit and by treatment group.

Central laboratory data along with the normal ranges when applicable will be listed. Local laboratory data will not be summarized but will be listed.

3.4.3.1. Vital Signs

Vital sign parameters to be summarized include: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), respiration rate (breaths/min), temperature (C), and pulse rate (beats/min) and will be assessed at all visits in Part 2. Height will be collected at screening. Weight (kg) will be collected at scheduled visits (refer to Protocol for Schedule of Assessments).

Vital signs (actual values and CFB for continuous parameters) will be descriptively summarized by visit and by treatment group.

Selected vital signs have PCS categories defined in Part 1 SAP and will be tabulated by visit and overall post-baseline visit by treatment group.

3.4.4. Electrocardiogram Parameters

Local ECGs will be analyzed from a clinical safety basis (without intensive QT analysis) for Part 2 data. Local ECG parameters to be summarized include QT, QTcF, PR, and QRS intervals in msec and heart rate (beats /min). Means of triplicate measurements will be used for this summary, excluding 0 values. If there is at least 1 but less than 3 available measurements with non-zero values at a given timepoint, then mean will be calculated over these available values. If there are no available measurements with non-zero values at a given timepoint, the mean will be considered missing.

Average values and CFB on the averaged values for ECG parameters will be summarized separately by pre- and post-infusion and by treatment group.

Clinical interpretation of ECG tracings will be summarized by frequency and percentage of participants in each category.

Shift tables from baseline to post-baseline visit, and worst post-baseline visit will be provided separately by measurement time point (pre- and post-infusion) by visit and by treatment group.

PCS for ECG parameters will be summarized in a similar manner as the clinical judgment described previously. PCS criteria are listed in Part 1 SAP.

3.4.5. Physical and Neurological Examination

Clinically significant Physical and Neurological Examination abnormalities are captured as part of Medical History or AEs; therefore, no additional summaries or listings will be provided.

3.4.6. Magnetic Resonance Imaging

MRI abnormalities are captured as part of Medical History or AEs.

MRI findings in Part 2 will be provided in a listing for any participants that have had any documentation of lesions (eg, microhemorrhages, white matter disease involvement).

3.5. Other Safety Assessments

3.5.1. Pregnancy Test

Urine and/or serum pregnancy tests will be presented in data listings for all women of child-bearing potential, for Part 2 data.

3.5.2. Impacts Due to COVID-19

A listing will be provided for the impact on participant visits due to COVID-19 as documented in the eCRF, for Part 2 data.

3.6. Immunogenicity Analyses

Similar analyses to those described in Part 1 SAP will be performed by groups, for the data in Part 2, using the SAF-Part2.

3.7. Exploratory Analyses

3.7.1. Efficacy Analyses

All clinical efficacy endpoints listed below will be summarized by descriptive statistics, by actual values and CFB (using the Part 2 baseline except for CGI-I) at each visit in Part 2, by groups, by Part1 baseline symptomatic status, using the FAS-Part2. The CGI-I is used to rate how much a participant's disease has improved or worsened relative to the Part 1 baseline, not the Part 2 baseline.

- CDR plus NACC FTLD-SB
- CDR plus NACC FTLD-GS
- CGI-S
- FRS
- CGI-I
- RBANS

These efficacy endpoints, including CDR plus NACC FTLD-SB, CGI-S, FRS logit score, CGI-I, and RBANS total scale score, will be summarized by descriptive statistics, by actual values and CFB (using the Part 1 baseline except for CGI-I) at each visit in Part 1 and Part 2, by the

Placebo-Latozinemab and Latozinemab-Latozinemab group, using the FAS-symptomatic. A similar analysis will be performed for FAS-Part2-symptomatic. In addition, a longitudinal plot of mean (+/- SE) change from Part 1 baseline will be presented, from Week 24 to Week 96 for FAS-symptomatic and from Week 96 to Part 2 Week 96 for FAS-Part2-symtomatic.

Additionally, these efficacy endpoints, including CDR plus NACC FTLD-SB, CGI-S, FRS logit score, CGI-I, and RBANS total scale score, will be analyzed using Mixed Models for Repeated Measures (MMRM), including all post-baseline data from both Part 1 and Part 2, and by the Placebo-Latozinemab group and Latozinemab-Latozinemab group, using the FAS-symptomatic. This analysis will follow a methodology similar to that of Part 1 SAP as outlined below but will allow for different covariance matrix for each group. For CGI-I, the MMRM will be conducted in a similar fashion with the difference being that the baseline CGI-S as covariate in the model.

The estimator will be an MMRM model with the CFB (using the Part 1 baseline) as the outcome variable, using all post-baseline data up to the last visit where the total number of subjects with available CDR plus NACC FTLD-SB is no less than 10. The model will include fixed-effects of treatment group, Part 1 baseline, log-10 transformed Part 1 baseline serum NfL concentration, time point and time point-by-treatment interaction. The model will treat missing data as MAR. An unstructured covariance structure will be used for within-participant residuals, and the model will be estimated using REML with robust "sandwich" variance estimation. In case of model convergence issues, the Fisher scoring algorithm will be used (using the option SCORING of PROC MIXED) to obtain initial estimates of the unstructured variance-covariance matrix. If this fails to converge, then additional residual covariance structures will be explored with robust (empirical) variance estimates following the testing order as specified in Appendix 1 of Part 1 SAP.

The within-treatment group least squares mean (LSMean) of CFB and corresponding SE and 95% CI for each post-baseline visit will be reported. Treatment group-specific LSMeans (±SE) over time will be plotted.

3.7.2. Quality of Life: EuroQOL-5 Dimensions

The EQ-5D VAS will be summarized descriptively by actual value, CFB (using Part 2 baseline), at each visit in Part 2, by treatment group, using FAS-Part2-symtomatic.

For categorical ratings of each of the EQ-5D domains, the frequency and proportion of reported problems will be reported by visit in Part 2 and treatment group, using FAS-Part2-symtomatic.

Additionally, an MMRM analysis will also be conducted with similar attributes as outlined in Section 3.7.1 for the CFB (using Part 1 baseline), in EQ-5D VAS score, including all post-baseline data from both Part 1 and Part 2, using the FAS-symptomatic.

3.7.3. Quality of Life: Zarit Burden Interview

A descriptive summary of the ZBI, change from Part 2 baseline ZBI, and the qualitative interpretation (defined in Part 1 SAP) will be reported at each visit in Part 2 by treatment group, using the FAS-Part2-symptomatic.

Additionally, an MMRM analysis will also be conducted with similar attributes as outlined in Section 3.7.1 for the CFB (using Part 1 baseline), in ZBI score, including all post-baseline data from both Part 1 and Part 2, using the FAS-symptomatic.

3.7.4. Pharmacoeconomic: Resource Utilization in Dementia-Lite Version

A subset of items focused on objective measures of health care utilization by the participant (eg, hospital admissions, ER visits) and time spent by the caregiver (eg, assisting the participant with activities of daily living, supervision) will be summarized using descriptive statistics This summary will present actual values by visit in Part 2 and by treatment group, using the FAS-Part2-symptomatic.

3.7.5. Fluid Biomarker Analyses

Please refer to Part 1 SAP for the list of fluid biomarkers to be included in the biomarker analyses. Fluid biomarkers (blood-based and CSF) will be summarized descriptively by actual values (untransformed), CFB (using Part 2 baseline), PCFB (using Part 2 baseline), and log-10 transformed values, at each visit in Part 2, by groups, using the FAS-Part2 and by Part 1 baseline symptomatic status.

Analysis of Blood-based Biomarkers

Blood-based biomarkers (plasma PGRN, serum NfL and plasma GFAP), will be summarized by descriptive statistics, by actual values (untransformed), CFB (using Part 1 baseline), PCFB (using Part 1 baseline), and log-10 transformed values, at each visit in Part 1 and Part 2, by the Placebo-Latozinemab and Latozinemab-Latozinemab group, using the FAS-symptomatic. A similar analysis will be performed for FAS-Part2-symtomatic. In addition, a longitudinal plot of geometric mean with error bars of observed fold change from Part 1 baseline will be presented, from Week 8 to Week 96 for FAS-symptomatic and from Part 2 Week 0 to Part 2 Week 96 for FAS-Part2-symtomatic. Error bars are calculated as (geometric mean / geometric SD, geometric mean * geometric SD), with geometric mean and geometric SD calculated as the antilog of the mean and SD of the change from Part 1 baseline of the log10-transformed biomarker concentrations.

In addition, an MMRM analysis will also be conducted with similar attributes as outlined in Section 3.7.1, unless specified otherwise below.

The analysis will include all post-baseline data from both Part 1 and Part 2, by groups, using the FAS-symptomatic. The MMRM analysis will model the change from Part 1 baseline of the log-10 transformed concentration for each blood-based biomarker. The log-10 transformed biomarker value at Part 1 baseline, and Part 1 baseline CDR plus NACC FTLD-SB score will be included as covariates in the model. The LSMeans (based on log-10) for each treatment group and associated 95% CIs will be reported for each assessed time point. Treatment group-specific LSMeans (±SE) over time will be plotted. For ease of interpretation, LSMeans will be further converted to original scale as a percentage.

3.7.6. Magnetic Resonance Imaging Biomarker Analyses

MRI parameters will be summarized by baseline volume and post-baseline atrophy (ie, change in volume since Part 1 baseline) measurements, at each visit in Part 1 and Part 2, by the Placebo-Latozinemab and Latozinemab-Latozinemab group, using the FAS-symptomatic. A similar analysis will be performed for FAS-Part2-symtomatic. In addition, longitudinal plot of mean (+/- SE) change from Part 1 baseline will be presented, from Week 48 to Week 96 for FAS-symptomatic and from Part 2 baseline to Part 2 Week 96 for FAS-Part2-symptomatic.

In addition, an MMRM analysis will be conducted with similar attributes as outlined in Section 3.7.1 for the CFB (using Part 1 baseline), including all post-baseline data from both Part 1 and Part 2, by groups, using the FAS-symptomatic. The model will include Part 1 baseline regional bilateral volume, log-10 transformed serum NfL at Part 1 baseline, Part 1 baseline CDR plus NACC FTLD-SB score, and age at Part 1 baseline as covariates.

The analyses above will be restricted to 4 vMRI bilateral ROIs (frontal, temporal, parietal and ventricular) as specified in Part 1 SAP.

3.7.7. Winterlight Labs Speech Analysis (Optional Assessment)

Analyses of Winterlight Lab Speech data may be conducted and will be covered in a separate exploratory analysis plan, if sufficient data are available to conduct an analysis.

3.7.8. PK and PK/PD Analyses

The following planned analyses will only apply to listing and summary of serum and CSF PK concentration data in Part 2. A separate analysis plan will be developed to describe population PK and exposure-response analyses.

Serum and CSF concentration at each study visit and timepoint will be presented in data listings. Serum and CSF concentration data will be summarized by study visit and timepoint for the PK-Part2 using descriptive statistics: number of participants with non-missing data (n), mean, SD, CV, median, minimum, maximum, geometric mean, and geometric CV. For summary statistics and mean plots, all concentrations that are below LLOQ (BLQ) before first Part 2 dose will be set to 0 in the Placebo-Latozinemab arm and to missing in the Latozinemab-Latozinemab arm, and after first Part 2 dose will be set to missing.

3.8. Subgroup Analyses of Interest

There will be no subgroup analyses for Part 2 data due to the sample size.

3.9. Analysis Considerations for At-risk Participants

Given the small sample size of at-risk participants in Part 2, summary statistics will be provided for at-risk participants for selected endpoints, as described above (efficacy and fluid biomarker endpoints).

4. INTERIM ANALYSIS

There is no interim analysis specified in the protocol, however Part 2 data up to the CCoD for the Part 1 database lock will be analyzed according to this SAP and will be submitted for health authority review in the initial marketing application submissions. Given the sample size reaching Part 2 Week 96, analyses based on the MMRM model will not be performed at that time.

A final analysis of Part 2 will be conducted when all participants complete the study and database is locked for the entire study.

5. CHANGES FROM AND ADDITIONS TO METHODS PLANNED IN THE PROTOCOL

None for Part 2.

6. SUPPORTING DOCUMENTATION

APPENDIX 1. PLANNED DATA INCLUSIONS (PART 1 AND PART 2) FOR ENDPOINTS ANALYSES

	Part1 + Part 2 (Use Part 1 Baseline Where Applicable)		**Part 2 (Use Part 2 Baseline Where Applicable)**		
Group (Data Part)	**Placebo-Latozinemab** (Part 1 + Part 2)	**Placebo-Latozinemab** (Part 1 + Part 2)	**Latozinemab-Latozinemab** (Part 2)	**Placebo-Latozinemab** (Part 2)	**Total** (Part 2)
Endpoints Analyses					
COAs, Quality of Life, Fluid Biomarker	x	x	x	x	x
MRI Biomarker	x	x			
Safety			x	x	x
Demographic and Baseline Characteristics, Study Drug Exposure, Concomitant Medications/Procedures			x	x	x
PK, PD, Immunogenicity, Pharmacoeconomic			x	x	x

Document Approvals

Approval Task Verdict: Approve	Jinglin Zhong, [redacted] Management Approval 30-Sep-2025 19:34:24 GMT+0000

Approval Task Verdict: Approve	Arthur Mayorga, [redacted] Author Approval 30-Sep-2025 19:38:02 GMT+0000