Alector Inc.

AL001-2

A Phase 2, Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AL001 in Heterozygous Carriers of *Granulin* or *C9orf72* Mutations Causative of Frontotemporal Dementia

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Final Statistical Analysis Plan

Version 3.0

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List of Abbreviations

ADA	Antidrug antibody
AE	Adverse event
aFTD-*GRN*	Asymptomatic frontotemporal dementia carriers heterozygous for *granulin* mutations
ALT	Alanine aminotransferase
ANC	Absolute neutrophils count
AST	Aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
AUC_{ss}	Area under the concentration-time curve at steady state
BP	Blood pressure
bvFTD	Behavioral variant frontotemporal dementia
CDR	Clinical Dementia Rating Scale
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clincal Global Impression of Severity
CI	Confidence interval
C_{max}	Maximum observed concentration
CNS	Central nervous system
COA	Clinical outcome assessment
CSF	Cerebrospinal fluid
CSR	Clinical study report
C_{trough}	Trough concentration
CTT	Color Trails Test
CV	Coefficient of variation
D-KEFS	Delis-Kaplan Executive Function System
DTI	Diffusion tensor imaging
ECG	Electrocardiogram
eCRF	Electronic case report form
FCRS	Frontotemporal Dementia Clinical Rating Scale
FDA	US Food and Drug Administration
FRS	Frontotemporal Dementia Rating Scale
FTD	Frontotemporal dementia
FTD-*C9orf72*	Symptomatic frontotemporal dementia patients with *C9orf72* hexanucleotide repeat expansion mutations
FTD-*GRN*	Symptomatic frontotemporal dementia patients heterozygous for *granulin* mutations
FTLD	Frontotemporal lobar degeneration
FTLD-FUS	Frontotemporal lobar degeneration – immunoreactive to the fused in sarcoma protein
FTLD-TDP	Frontotemporal lobar degeneration – transactive response DNA-binding protein 43
GCP	Good Clinical Practice
GRN	*Granulin*
ICF	Informed consent form
ICH	International Council for Harmonisation

IEC	Independent ethics committee
IRB	Institutional review board
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model of repeated measures
MMSE	Mini-Mental Status Exam
MRI	Magnetic resonance imaging
mRNA	messenger ribonucleic acid
NFL	Neurofilament-light
NPI	Neuropsychiatric Inventory
OLE	Open-Label Extension
PD	Pharmacodynamic(s)
PE	Physical examination
PGRN	Progranulin
PK	Pharmacokinetic(s)
PPA	Primary progressive aphasia
PT	Preferred term
q4w	Every 4 weeks
QTcF	QT interval corrected using Fridericia formula
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
SAE	Serious adverse event
SAP	Statistical analysis plan
Sheehan-STS	Sheehan Suicidality Tracking Scale
SOC	System organ class
TDP-43	DNA-binding protein 43
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
[redacted]	[redacted]
WBC	White blood cell
WGS	Whole genome sequencing
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary
WLA	Winterlight Lab Speech Assessment
WOCBP	Woman of childbearing potential

1. Introduction

This document outlines the statistical methods to be implemented during the analysis of data collected within the scope of Alector Inc. protocol AL001-2 version 4.0, dated 04 Feb 2021 (A Phase 2, Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AL001 in Heterozygous Carriers of Granulin or C9orf72 Mutations Causative of Frontotemporal Dementia) and the previous version 3.2 United Kingdom, dated 23 November 2020, version 3.1, dated 13 July 2020, version 3.0, dated 02 June 2020, version 2.0, dated 26 September 2019 and the original protocol version 1.0, dated 09 April 2019. The purpose of this plan is to provide specific guidelines for the analyses. Any deviations from these guidelines will be documented in the clinical study report (CSR). The analyses described in this plan are considered a priori, in that they have been defined prior to database lock. Any analyses performed subsequent to database lock will be considered post-hoc and exploratory post-hoc analyses will be identified in the CSR.

1.1. Objectives and Endpoints

Table 1: Part 1 (Treatment Period): Study Objectives and Endpoints

	Objective(s)	Endpoint(s)
Primary	The primary objective of the treatment period of the study is to evaluate the safety and tolerability of IV administration of AL001 over 96 weeks in asymptomatic and symptomatic carriers of a GRN mutation causative of FTD and in symptomatic carriers of a *C9orf72* mutation causative of FTD.	*Primary Safety Endpoints:* To assess the potential effect of cumulative exposure on the safety profile of AL001, the following will be evaluated by dose, such as by using tertiles of the actual dose (normalized to weight) received: • Incidence, nature, and severity of AEs and SAEs • Incidence of treatment discontinuations and study discontinuations due to AEs • Physical examination abnormalities • Neurological examination abnormalities • Changes in vital signs from baseline over time • Changes in ECGs from baseline over time • MRI abnormalities after dosing relative to baseline • Changes in clinical laboratory tests from baseline over time • Sheehan Suicidality Tracking Scale (Sheehan-STS) • Incidence of ADAs to AL001
Secondary	The secondary objectives of the treatment period of the	

	study are to evaluate the effect of IV administration of AL001 over 96 weeks in asymptomatic and symptomatic carriers of a GRN mutation causative of FTD and in symptomatic carriers of a *C9orf72* mutation causative of FTD on the following:	
	Secondary PK Objective: • PK	*Secondary PK Endpoints:* • Serum concentration of AL001 at specified time points • AL001 PK parameters (if data permit) o C_{max} o C_{trough} o AUC_{ss}
	Secondary PD Biomarker Objectives: • Longitudinal plasma and CSF PGRN concentration levels • Longitudinal levels of Sortilin in WBCs	*Secondary PD Biomarker Endpoints:* • The overall change from baseline in PGRN in CSF • The overall change from baseline in PGRN in plasma • The overall change from baseline in Sortilin in WBCs in plasma
Exploratory	The exploratory objectives of the treatment period of the study are to assess the effect of IV administration of AL001 over 96 weeks in asymptomatic and symptomatic carriers of a GRN mutation causative of FTD and in symptomatic carriers of a *C9orf72* mutation causative of FTD on the following:	
	Exploratory PD Biomarker Objectives: • Longitudinal blood, plasma, and CSF concentration levels of exploratory biomarkers of neurodegeneration, lysosomal function, and glial activity • MRI measures to evaluate changes in the brain • Global and regional brain MRI atrophy measures	*Exploratory PD Biomarker Endpoints:* • The overall change from baseline in exploratory biomarkers of neurodegeneration, lysosomal function, and glial activity in blood, plasma, and CSF • Global and regional brain MRI atrophy measures • Correlations among exploratory fluid biomarkers, imaging measures, and COAs

	• Correlations among exploratory fluid PD biomarkers, imaging PD measures, and COAs	
	Exploratory Clinical Objectives: • Clinical progression as measured by COAs	*Exploratory Clinical Endpoints:* The overall change from baseline on the scores of the instruments in the COAs • Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center Frontotemporal Lobar Degeneration Behavior and Language Domains (Clinical Dementia Rating (CDR®) plus NACC FTLD) • Frontotemporal Dementia Rating Scale (FRS) • Clinical Global Impression of Improvement (CGI-I) • Clinical Global Impression of Severity (CGI-S) • Color Trails Test (CTT) Part 2 • Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) • Winterlight Labs Speech Assessments (WLA; for participants who agree to participate in these optional assessments only)

Table 2: Part 2 (Optional Open-Label Extension (OLE)): Objectives and Endpoints

	Objective(s)	**Endpoint(s)**
Primary	The primary objective of the OLE period of the study is to assess the long-term safety and tolerability of AL001 in participants who have completed 96 weeks of treatment on Part 1 of the study.	• Incidence, nature, and severity of AEs and SAEs • Incidence of treatment discontinuations and study discontinuations due to AEs • Physical examination abnormalities • Neurological examination abnormalities • Changes in vital signs from baseline over time • Changes in ECGs from baseline over time • MRI abnormalities after dosing relative to baseline • Changes in clinical laboratory tests from baseline over time • Sheehan-STS

		• Incidence of ADAs to AL001
Exploratory	COAs, correlative assessments (e.g., biomarker) 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 AL001 in participants who have completed 96 weeks of treatment on Part 1 of the study on the following:	
	• PK	Serum concentration of AL001 at specified time points • AL001 PK parameters (if data permit) o C_{max} o C_{trough} o AUC_{ss}
	• Longitudinal plasma and CSF PGRN concentration levels	• The overall change from baseline in PGRN in plasma
	• Longitudinal blood, plasma, and CSF concentration levels of exploratory biomarkers of neurodegeneration, lysosomal function, and glial activity	• The overall change from baseline in exploratory biomarkers of neurodegeneration, lysosomal function, and glial activity in blood, plasma, and CSF
	• Magnetic resonance imaging (MRI) measures to evaluate changes in the brain	• Global and regional brain MRI atrophy measures
	• Correlations among exploratory fluid PD biomarkers, imaging PD measures, and clinical outcome assessments (COAs)	• Correlations among exploratory fluid biomarkers, imaging measures, and COAs
	• Clinical progression as measured by COAs	The overall change from baseline on the scores of the instruments in the COAs • CDR® plus NACC FTLD • FRS • CGI-I • CGI-S • CTT Part 2 • RBANS

		• Winterlight Labs Speech Assessments (for participants who agree to participate in these optional assessments only)

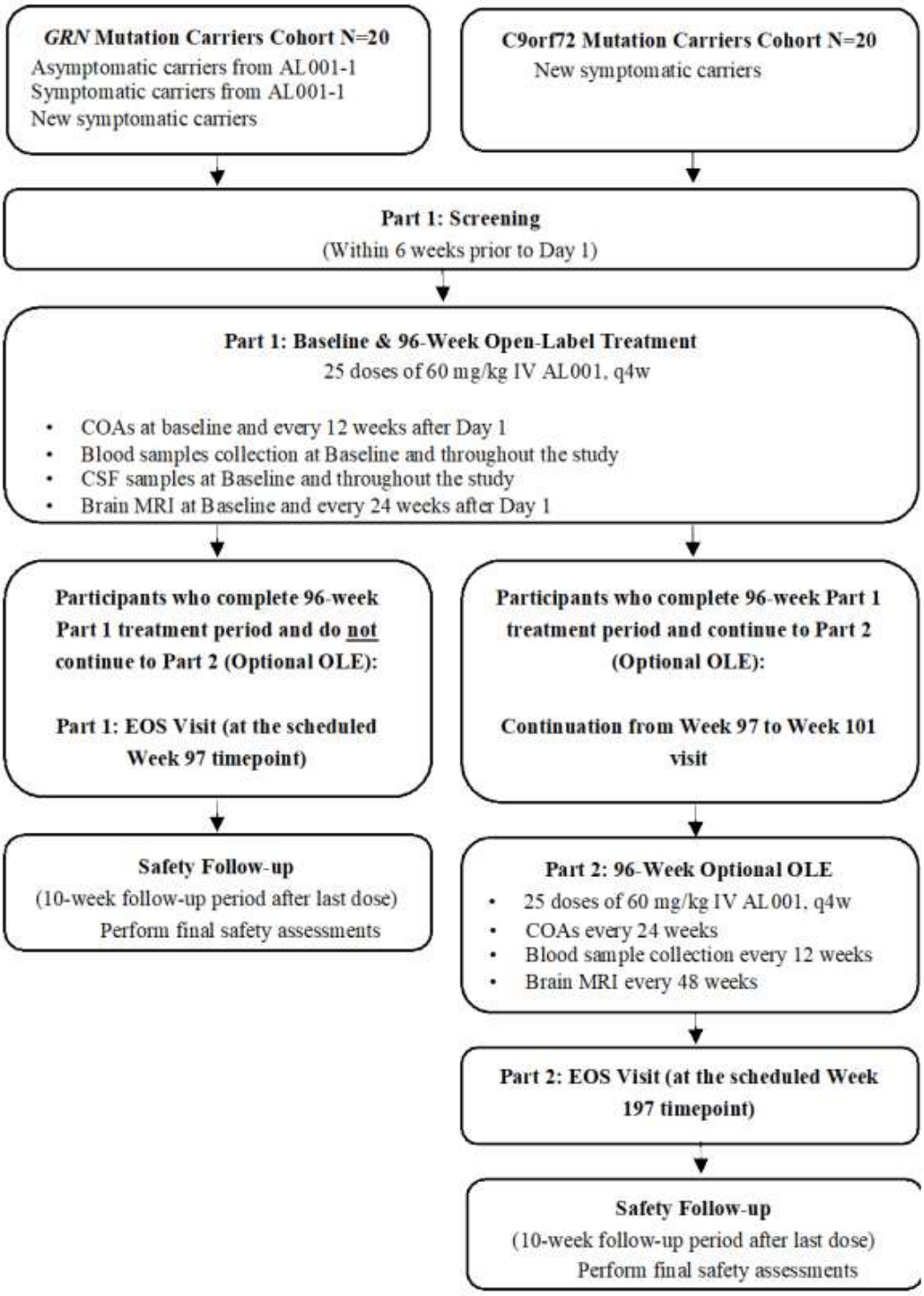
1.2. Study Design

This is a Phase 2, multicenter, open label study evaluating the safety, tolerability, PK, PD, and effect on COAs of AL001 administered intravenously (60 mg/kg, q4w) in asymptomatic and symptomatic carriers of loss-of-function GRN mutations causative of FTD and in symptomatic carriers of C9orf72 hexanucleotide repeat expansion mutations causative of FTD. This study has two parts: A phase 2 open-label treatment period (Part 1), followed by an optional open-label extension (OLE) period (Part 2).

Part 1 is a 96-week evaluation of the safety, tolerability, PK, PD, and clinical effect of AL001 administered intravenously (60 mg/kg, every 4 weeks [q4w]), for a total of 25 doses (96-week dosing period), in asymptomatic and symptomatic carriers of loss-of-function GRN mutations causative of FTD, and in symptomatic carriers of C9orf72 hexanucleotide repeat expansion mutations causative of FTD.

Part 2 is an optional OLE for eligible participants who have completed the 96-week Part 1 treatment period. The OLE period will evaluate the long-term safety and tolerability of AL001 administered at the same dose and regimen as Part 1 (60 mg/kg, q4w), for up to a total of 25 doses (96-week optional OLE period).

Figure 1-1 Overview of Study Schema



Abbreviations: COA, clinical outcome assessment; CSF, cerebrospinal fluid; *GRN*, granulin; IV, intravenous; MRI, magnetic resonance imaging; PD, pharmacodynamic; q4w, every 4 weeks.

2. General Statistical Considerations

All data collected from enrolled participants, excluding screen failures, will be presented in data listings. Data from participants excluded from an analysis set will be presented in the data listings but not included in the calculation of summary statistics for the corresponding analysis set.

Data from Part 1 and Part 2 will be combined and will not be analyzed separately.

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of participants, mean, standard deviation [SD], median, minimum, maximum, and 90% or 95% confidence interval [CI] where applicable). All summaries will be presented by the three cohorts [asymptomatic FTD-*GRN* (aFTD-GRN), symptomatic FTD-*GRN* (FTD-*GRN*), symptomatic FTD-*C9orf72* (FTD-*C9orf72*)] and All Participants.

Baseline will be defined as the last non-missing assessment, including repeated and unscheduled measurements, prior to the start of first study drug administration.

Due to the high rate of participant attrition over the study duration and small FTD cohort sizes, time points beyond week 49 will not be included in the cohort level summary of the figures.

All CIs will be 2-sided and performed using a 5% significance level except for PK parameters for which, 90% CI and geometric mean will be used. All p-values will be presented to 3 decimal places and values less than 0.001 or greater than 0.999 will be presented as <0.001 and >0.999, respectively. As the objectives of the study are exploratory in nature no adjustments for multiplicity will be made.

No formal significance testing will be performed.

Analysis visit windows will be applied for COA and Biomarker analysis. A detailed explanation about the analysis visit windows will be described in the specific section of each analysis,

2.1. Sample Size

Part 1 (Treatment Period)

The primary objective of Part 1 of this study is to assess the safety profile of repeat dosing of AL001 in three FTD cohorts: aFTD-*GRN*, FTD-*GRN*, and FTD-*C9orf72* participants. Descriptive statistics will be used to assess clinically significant associated findings (for example, study-drug related AEs leading to study drug discontinuation or study-drug related SAEs). The Part 1 sample size of 40 participants was chosen based on feasibility; however, the probability of detecting at least 1 clinically significant associated finding will be explored. When the probability of a clinically significant associated finding for a single participant is 0.1%, 1%, 5%, and 10%, then with a sample size of 40 participants, the probability of detecting at least

1 clinically significant associated finding across all participants is 3.9%, 33.1%, 87.1%, and 98.5%, respectively.

Part 2 (Optional OLE)

It is estimated that up to 40 participants from Part 1 of the study will be eligible to continue with Part 2 of the study. Part 2 is optional for participants, and at the discretion of the investigator.

2.2. Randomization and Blinding

This is an open label study where all participants will receive AL001, and doses are not concealed; randomization and blinding, therefore, are not required.

2.3. Analysis Populations

The following analysis sets will be used in the statistical analyses:

2.3.1. Enrolled Population

The enrolled population will consist of all participants who signed the ICF.

2.3.2. Safety Analysis Population

The safety analysis population will consist of all participants who received at least 1 dose of AL001. The safety analysis population will be used for all safety and COA summaries.

2.3.3. PK Analysis Population

The PK analysis population will include all participants in the safety population who had adequate assessments for determination of at least 1 PK parameter. The PK analysis population will be used for PK parameter summaries.

2.3.4. Full Analysis Population

The Full analysis population will include all participants in the safety population who had both a baseline and at least 1 postdose PD assessment. The Full analysis population will be used for summaries of all PD and PD biomarker summaries.

3. Participant Disposition and Protocol Deviations

3.1. Disposition

Participant disposition will be summarized. The number of participants and reasons for study discontinuation, reasons for study drug discontinuation, and the number of participants in each analysis population will be presented.

Participant disposition data and membership in analysis populations for participants in the Enrolled population will be presented in data listings.

Data collected for participants who failed screening will not be presented in any summaries or data listings.

3.2. Protocol Deviations

A protocol deviation occurs when the participant, investigator, or Alector (or designee) fails to adhere to protocol requirements. Major protocol deviations are the ones that affect the participants' safety or the primary endpoint (safety). Major protocol deviations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Failure to comply with GCP guidelines will also result in a major protocol deviation; Alector will determine if a major protocol deviation will result in withdrawal of a participant.

Major protocol deviations will be summarized for the Safety population, and all protocol deviations will be presented in a data listing, including the categorization of the deviation as major or minor.

4. Demographics and Baseline Characteristics

Qualitative data (eg, genotyping data, diagnostic characterization) will be summarized in contingency tables, and quantitative data (eg, age) will be summarized using quantitative descriptive statistics.

4.1. Demographics

Demographic information (year of birth, age, sex, race) will be recorded at screening, unless disallowed by local regulatory agencies. Demographics (including but not limited to age, age group (19-64, >=65), sex, and race, if allowable per local regulatory authorities) and baseline characteristics will be presented in summary tables.

For US, UK, and Canadian participants who will be performing the optional WLA, additional demographic information will be collected. The optional WLA data will be analyzed and reported outside of this SAP.

Demographic information collected at Screening will be summarized by group and overall for all participants in the safety population and listed. Descriptive statistics will be calculated for the following continuous demographic characteristics: age (years), screening and Day 1 pre-dose weight (kg), screening height (cm), and screening body mass index (BMI) (kg/m2). Frequency counts will be tabulated for the categorical variables sex, race, and ethnicity.

4.2. Diagnostics Characterization

A diagnostic characterization form will be completed in the electronic case report form (eCRF) only at screening, week 97 and week 197 (if applicable for symptomatic participants in the optional Part 2 OLE). It will also be completed for any asymptomatic participant who becomes symptomatic during the course of the study; for these participants, the diagnostic characterization form will be completed only at the first visit in which they exhibit clinical symptomatology.

Diagnostic characterization data will be summarized for the Safety population and will be presented in a data listing.

4.3. Medical History

All relevant medical history and information regarding underlying diseases will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version to be delineated in the CSR.

Medical history data will be summarized by system organ class (SOC), preferred term (PT) for the Safety population. Medical history data will be presented in a data listing.

4.4. Admission Criteria Deviation

Admission criteria deviation data (violations of the inclusion/exclusion criteria) will be presented in a data listing.

4.5. Pharmacogenomic Measurements

A blood sample will be collected during Part 1 at screening for DNA extraction to enable analysis via whole genome sequencing (WGS) to identify common and rare genetic variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with susceptibility to developing AEs, or can increase the knowledge and understanding of disease biology.

Pharmacogenomic data will not be analyzed or reported in the CSR.

5. Treatments and Medications

5.1. Prior and Concomitant Medications

All concomitant medications used by a participant from informed consent through Study Completion or ET visit, whichever is later, will be recorded in the participant's eCRF and coded using the World Health Organization Drug Dictionary (WHO-DD), version to be delineated in the CSR. The minimum requirement is that drug name, total daily dose, route, frequency of dosing, indicated use, and the dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, vaccines, topical medications, and over-the-counter medications. Any changes in concomitant medications also will be recorded in the participant's eCRF.

Any restricted medication must have been stopped as required by the study inclusion and exclusion criterion (Protocol Sections 4.2.1 and 4.2.2 respectively); participants who start these medications during the study may be withdrawn from study treatment at the discretion of the sponsor's medical monitor.

A medication will be considered as concomitant if the end date and time of administration is after start of administration of study drug. 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. A medication will be considered as prior if the start and stop date and time of administration is prior to the start of administration of study drug. A medication started prior to study drug and continuing during the study will be considered as concomitant.

The number and percentage of participants taking prior and concomitant medications will be summarized for each level of ATC (Anatomical-Therapeutic-Chemical) and preferred drug name, and alphabetically sorted for participants in the Safety population.

Prior and concomitant medications will be presented in a data listing.

5.2. Medical and Surgical Treatment Procedures

Medical and surgical treatment procedure data will be presented in a data listing.

5.3. Study Drug Administration

Study drug administration data will be summarized for the Safety population. The summary will include duration of exposure to study drug (in days), the number of doses received, treatment compliance, number of doses interrupted, discontinued, and total dose (mg) received.

Duration of exposure to study drug (days) is defined as the total number of days a participant is exposed to AL001 and will be calculated as the total number of days from the first dose date (Study Day 1) to the last dose date + 28 days, regardless of any temporary interruptions in study drug administration. 28 days is the study treatment administration (IV) interval.

Treatment compliance will be defined as the total cumulative received dose (mg/kg) divided by the total cumulative expected dose (mg/kg) up to the last dose, and then multiplied by 100. The total cumulative expected dose will be the sum of the expected doses while they are on study treatment across all planned study days, up to the date of withdrawal, if participant discontinued study drug early.

The function is as follow:

Treatment Compliance=100×(total cumulative received dose (mg/kg))/(total cumulative expected dose (mg/kg))

Study drug administration data will be presented in a listing. Any drug administration interruption and reasons will be listed.

6. Safety Analysis

All analyses of safety data will be conducted using the Safety population. All safety data will be listed.

6.1. Adverse Events

An AE is defined as any untoward medical occurrence in a participant enrolled into this study regardless of its causal relationship to study drug.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug, or any event already present that worsens in either intensity or frequency after exposure.

An imputation will be performed for AEs with incomplete (partial) dates to determine whether an AE is treatment emergent.

For AEs with a partial start date:

- If the year is unknown, then the AE start date will be the date of first dose.
- If the month is unknown, then:
    - If the year matches the year of the first dose date, then the month and day of the first dose date will be imputed.
    - Otherwise, 'January' will be assigned.
- If the day is unknown, then:
    - 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.
    - Otherwise, '01' will be assigned.

For AEs with a partial end date:

- If the year is unknown, then the date assigned will be the last visit date.
- If the month is unknown, then the month from the last visit date will be assigned.
- If the day is unknown, then the last day of the month will be assigned.

If the imputation approach results in a start date that is after a known end date, then the start date will be set to the day before the end date. If the imputation approach results in an end date that is before a known start date, then the end date will be set to the day after the start date.

An AE with completely missing onset 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 to be 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.

The relationship of AE to study drug will be classified as Not Related or Related by the Investigator. If the relationship information is missing, the AE will be considered Related in the summary but will be presented as missing in the listings.

The severity of AEs will be classified as Mild, Moderate, Severe, Life-threatening, or Death by the Investigator. If the severity information is missing, the AE will be considered Severe in the summary but will be presented as missing in the listings.

Adverse Events will be coded by SOC and PT according to MedDRA, version to be delineated in the CSR.

All summary tables will include counts and frequency of participants and number of events. Subject incidence rate of AEs will be summarized by SOC and PT and for PT only. The summary will be provided separately by overall descending incidence rate and then by alphabetical order. A separate summary will be provided by alphabetical order for SOC and PT. A participant with 2 or more occurrences for the same AE, the subject will be counted only once in that level using the worst severity (for the severity table) or the most related (for the relationship to study drug table). Percentages will be based upon the number of participants in the Safety population.

6.1.1. Incidence of Adverse Events

An overall summary of AEs will be presented and will include summaries for the following:

- Any TEAE
- Any Treatment-Related TEAE
- TEAEs by Severity
- Treatment-Related TEAEs by Severity
- Any SAE
- Any Treatment-Emergent SAE
- Any Treatment-Related TESAE
- Any TEAE Leading to Study Drug Discontinuation
- Fatal TESAE

In addition, all TEAEs will be summarized by SOC and PT.

6.1.2. Relationship of Adverse Events to Study Drug

Treatment-emergent AEs will be summarized by SOC, PT, and relationship to study drug.

Treatment-related AEs will be presented in a data listing.

6.1.3. Severity of Adverse Event

The TEAEs will be summarized by SOC, PT, and severity.

6.1.4. Serious Adverse Events

An SAE is defined as any event that

- results in death
- is immediately life threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Social hospitalization, defined as inadequate family support or care at the participant's primary residence resulting in participant hospitalization, will not be considered an SAE.

Serious TEAEs will be summarized by SOC and PT.

All SAEs will be presented in a data listing.

6.1.5. Adverse Events Leading to Study Drug Discontinuation

Treatment-emergent AEs leading to study drug discontinuation will be summarized by SOC and PT and will be presented in a data listing.

6.2. Clinical Laboratory Evaluations

Blood and urine samples that will be collected for clinical safety laboratory tests (chemistry, coagulation, hematology, urinalysis, serology, and pregnancy testing) are indicated in Table 8-1.

Laboratory assessment analysis will be performed at a central laboratory, with the exception of urine pregnancy testing which will be done at local laboratories.

Hematology, coagulation, serum chemistry, and urinalysis will be performed at the timepoints identified in Appendix 14.1, Appendix 14.2, Appendix 14.4 and Appendix 14.5. Additionally, unscheduled testing may be done during the study if medically indicated.

Abnormal clinical laboratory values will be flagged as either high or low (or normal or abnormal) based on the reference ranges for each laboratory parameter. The investigator will determine whether any of the abnormally high or low results are clinically significant or not clinically significant. Any clinically significant results will be entered into the eCRF as AEs, however the attribution of clinical significance will not be available in the data.

Actual results and change from baseline values for hematology, coagulation, serum chemistry, and urinalysis tests will be summarized by visit using descriptive statistics.

Shift from baseline in hematology, coagulation, serum chemistry, and urinalysis tests results relative to the reference range will be summarized by visit using the frequency count and percentage of participants in each category.

Refer to Section 4 for the definition of baseline.

All laboratory test results will be presented in data listings.

Table 8-1 Laboratory Assessments

Chemistry	**Coagulation**	**Hematology**	**Serology**
Total bilirubin Direct bilirubin Alkaline phosphatase gammaGT AST ALT LDH Creatine kinase Creatinine [a] Urea Uric acid Cholesterol HDL LDL Triglycerides Total protein Albumin Glucose Bicarbonate Inorganic phosphate Sodium Potassium Calcium Chloride Magnesium Lipase Apolipoprotein B100	PT INR aPTT	HbA1c Leukocytes Erythrocytes Hemoglobin Hematocrit Thrombocytes (platelets) MCV MCH MCHC *Partial automated differentiation*: Lymphocytes Monocytes Eosinophils Basophils Neutrophils [b] ANC [b]	anti-HCV anti-HIV HIV antigen HBsAg Total hepatitis B core antibody
	Urinalysis		**Pregnancy Test**
	Hemoglobin (blood urine) Ketones Glucose Protein Leukocyte esterase Nitrite pH Specific gravity Microscopic analysis [d] (sediment, erythrocytes, leukocytes, casts, crystals, epithelial cells, and bacteria)		Serum β-hCG or urine pregnancy test [c]

Abbreviations: ALT, alanine aminotransferase; ANC: absolute neutrophils count; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; β-hCG, β-human chorionic gonadotropin; gammaGT, gamma glutamyl transferase; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDL, high-density lipoprotein-cholesterol; HIV, human immunodeficiency virus; INR, international normalized ratio; LDH, lactate dehydrogenase; LDL, low-density lipoprotein-cholesterol; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; PT, prothrombin time.

[a] Creatinine (and calculation of glomerular filtration rate).

[b] ANC will be calculated at Screening only. Neutrophils will be assessed at all other time points.

[c] All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits prior to study drug administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
[d] Microscopic examination of the sediment if blood, protein, leukocytes esterase, or nitrite are positive on the dipstick.

6.3. Vital Signs and Weights Measurements

Vital sign measurements including systolic and diastolic BP, pulse rate, body temperature, respiratory rate, height, and weight will be collected at the timepoints identified in Appendix 14.1, Appendix 14.2, Appendix 14.4 and Appendix 14.5. Additional, unscheduled testing may be done during the study if medically indicated.

Supine systolic and diastolic BP, pulse, body temperature, and respiratory rate will be recorded after the participant has been resting for ≥5 minutes in the supine position.

Actual results and change from baseline values for vital signs will be summarized by visit and timepoint using descriptive statistics. Since the infusion is scheduled to last for approximately 60 minutes and Protocol section 5.5.4 allows for interruptions and rate reductions that would extend the infusion duration beyond 60 minutes, therefore; for summarization purposes all vital sign measurements collected during the infusion up to and including 60 minutes after the start of the infusion will be included. Vital sign measurements collected beyond 60 minutes after the start of the infusion and before the end of the infusion, in case that the infusion duration is beyond 60 minutes, will not be summarized. All vital sign measurements collected after the end of the infusion will be summarized. All vital signs data will be presented in a data listing.

Refer to Section 4 for the definition of baseline.

6.4. Triplicate 12-Lead Electrocardiograms

Triplicate 12-lead ECGs will be obtained after the participant has been in the supine position for ≥5 minutes. ECG measurements will be collected at the timepoints identified in Appendix 14.1, Appendix 14.2, Appendix 14.4 and Appendix 14.5.

All ECGs will be analyzed from a clinical safety basis (without intensive QT analysis). The clinical significance of ECG changes will be determined by the investigator after review of the ECG report in relation to the participant's medical history, PE, and concomitant medications and documented on the eCRF.

For summaries of quantitative triplicate 12-lead ECG parameters, the average of the triplicate 12-lead ECG measurements will be used for the determination of baseline and calculation of summary statistics.

For interpretation of triplicate 12-lead ECGs, baseline will be defined as the best case of the last non-missing triplicate measurements (including repeated and unscheduled measurements) before the start of first study drug administration. For calculation of post-dose summary statistics, the worst case of the non-missing triplicate measurements will be used. The order of interpretation

for 12-lead ECGs (best to worst case): Normal; Abnormal, Not Clinically Significant; Abnormal, Clinically Significant. Interpretations of Indeterminate, Not Evaluable, or Unknown will not be considered when determining the worst or best case.

Actual values and changes from baseline for quantitative ECG results will be summarized at each time point using descriptive statistics.

Shift from baseline in ECG interpretation and clinical significance will be summarized by visit using the frequency count and percentage of participants in each category.

In addition, the number (percentage) of subjects with at least 1 post-baseline abnormal ECG result in corrected QT interval calculated using Fridericia's formula (QTcF) interval, PR, QRS or HR will be summarized. Clinically abnormal ECG results will be categorized as follows:

Absolute QTcF interval prolongation:

• QTcF interval >450 msec

• QTcF interval >480 msec

• QTcF interval >500 msec

Change from baseline in QTcF interval:

• QTcF interval increases from baseline >30 msec

• QTcF interval increases from baseline >60 msec

• PR < 120 msec

• PR > 200 msec

• QRS < 60 msec

• QRS > 100 msec

• HR < 60 bpm

• HR > 100 bpm

All 12-lead ECG data will be presented in a data listing, 12-Lead Electrocardiogram data for participants with abnormal post-baseline result in QTcF interval will also be listed.

6.5. Physical and Neurological Examinations

A complete PE includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, and gastrointestinal systems. Breast, genital, and rectal examinations are not required, unless warranted in opinion of the

health care provider. The examination will be performed by a physician, or a nurse practitioner or physician's assistant under the supervision of a physician.

A limited, symptom-directed examination will be performed at all other specified time points, prior to study drug administration (if applicable) or as clinically indicated.

Abnormalities observed at screening will be recorded on the General Medical History and Baseline Conditions page of the eCRF. At subsequent visits, new or worsened clinically significant abnormalities will be recorded on the AE eCRF.

A complete neurologic examination will include the evaluation of consciousness, orientation, cranial nerves, motor and sensory system, coordination and gait, and reflexes. Changes from baseline abnormalities and changes from previous neurological examinations should be recorded at each subsequent neurologic examination. New or worsened abnormalities should be recorded as AEs on the AE eCRF if considered clinically significant.

Physical and neurologic examinations will be collected at the timepoints identified in Appendix 14.1, Appendix 14.2, Appendix 14.4 and Appendix 14.5.

Physical and neurological examinations will not be summarized or listed since exam results are only entered on the General Medical History and Baseline Conditions or AE pages of the eCRF

6.6. Sheehan Suicidality Tracking Scale (S-STS)

The S-STS will be performed at the timepoints identified in Appendix 14.1, Appendix 14.2, Appendix 14.4 and Appendix 14.5.

The S-STS is a brief scale designed to assess and monitor over time the core phenomena of suicidality. The Sheehan-STS is a 16-item scale that will be administered either by a clinician or participant through self-report. Each item in the Sheehan-STS is scored on a 5-point Likert scale (0=not at all, 1=a little, 2=moderately, 3=very, and 4=extremely). Any change in the Sheehan-STS score indicating the presence of suicidality should be immediately evaluated by the investigator and reported to the medical monitor. An AE should only be recorded if the investigator makes an evaluation and deems there to be suicidal ideation or behavior.

Actual results and change from baseline values for the S-STS Total Score will be summarized by visit using descriptive statistics.

All S-STS data will be presented in a data listing.

6.7. Immunogenicity

Immunogenicity sample collection for ADA will be collected at the timepoints indicated in Appendix 14.1, Appendix 14.2, Appendix 14.3, Appendix 14.4 and Appendix 14.5. Additional unscheduled assessments for participants with signs and symptoms of infusion-related reactions may be collected.

Antidrug antibody results will be summarized by visit using the frequency count and percentage of participants in each result category, as well as descriptive statistics of ADA titer by visit. The summary of ADA results will not include unscheduled assessments for participants with signs and symptoms of infusion-related reactions. Instead, data at baseline and the following visits for subjects with signs and symptoms will be listed separately. All immunogenicity data will be presented in a data listing.

6.8. Magnetic Resonance Imaging

Magnetic resonance imaging assessments will be performed at the timepoints indicated in Appendix 14.1, Appendix 14.2, Appendix 14.4 and Appendix 14.5.

MRI scans of the brain will be performed and centrally reviewed for assessment of safety (structural images). The safety assessment on MRI scans will be presented in a data listing.

7. Pharmacokinetics

7.1. Serum Pharmacokinetics Samples

Blood samples will be collected for assessment of serum concentrations of AL001. All serum PK samples should be drawn from the arm that is not used for the infusion on day of study drug administration. Specific information on PK sample collection, processing, storage, and shipment will be provided in a separate manual. Serum PK samples for AL001 will be collected at predose and at the end of infusion (within 15 minutes after the end of infusion) on weeks 1, 2, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 61 (3h post EOI and 24h also), 73, 85, 97, and 105 or study completion/ET for all participants.

Serum concentration and time deviation data at each study visit/timepoint will be presented in data listings by cohort (aFTD-GRN, FTD-GRN, FTD-C9orf72) at baseline in the Safety population. Serum concentration data will be summarized by study visit/timepoint and cohort at baseline for the PK analysis population using descriptive statistics: number of participants with non-missing data (n), mean, SD, CV, median, minimum, maximum, geometric mean, and geometric CV. All serum concentration values below the limit of quantification (BLQ) will be set to zero when calculating summary statistics.

Mean serum concentration versus nominal time profiles will be plotted on both linear and semilogarithmic scales for the PK analysis population by cohort at baseline. Individual serum concentration versus actual time profiles will be plotted on both linear and semilogarithmic scales for the Safety population.

7.2. CSF Pharmacokinetic Samples

Cerebrospinal fluid (CSF) samples will be collected via lumbar puncture prior to study drug administration (if applicable) at Screening, Week 25, Week 49, and Week 97 (or the EOT/EOS Visit) to evaluate CSF PK in Part 1 only. The Week 25 lumbar puncture may be adjusted as determined by Alector's review of exploratory PD biomarkers.

CSF concentration and time deviation data will be presented in data listings by study visit and cohort in the Safety population. CSF concentration data will be summarized by study visit and cohort for the PK population using descriptive statistics: number of participants with non-missing data (n), mean, SD, CV, median, minimum, maximum, geometric mean, and geometric CV. All CSF concentration values that are BLQ will be set to zero when calculating summary statistics.

Mean CSF concentration versus nominal time profiles will be plotted on linear scale and semilogarithmic scales for the PK population by cohort at baseline. Individual CSF concentration versus actual time profiles will be plotted on linear scale and semilogarithmic scales for the Safety population.

7.3. Serum Pharmacokinetic Parameters

The individual serum concentration versus actual time data for AL001 will be used to derive the following PK parameters if data permit, by standard noncompartmental methods using Phoenix® WinNonlin® Version 8.3 or higher (Certara USA, Inc., Princeton, NJ, USA).

Parameter	Description
C_{max}	Observed maximum serum concentration
C_{trough}	Trough serum concentration following each dose (equivalent to the trough concentration prior to each dose)
ARC_{trough}	Accumulation ratio using Ctrough: calculated as Ctrough for Week 61/Day 1

For the calculation of PK parameters, all serum concentrations that are BLQ prior to the first measurable concentration will be set to zero and treated as missing thereafter.

PK parameters will be summarized for the PK population by cohort in tables using the following descriptive statistics: n, arithmetic mean, SD, CV), geometric mean, geometric mean CV, 90% CI, minimum, median, and maximum. Individual PK parameters will be presented in data listings for the PK population.

Description of any needed population PK analysis will be provided in a separate analysis plan.

8. Pharmacodynamic Biomarkers

PD endpoints will be described and summarized by cohort at baseline and each timepoint, as will the percent change from baseline for each PD endpoint. PGRN will be evaluated in plasma and CSF samples.

8.1. Progranulin Plasma Samples

Blood samples will be collected for evaluation of levels of PGRN in plasma.

PGRN plasma samples will be collected prior to study drug administration on weeks 1, 2, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 61 (24 h also), 73, 85, 97, and 105 or study completion/ET for all participants.

The absolute value, absolute change, and percent change from baseline of plasma PGRN will be presented in data listings by cohort and timepoint for the Full Analysis population. Plasma PGRN concentration data will be summarized by cohort and timepoint for the Full Analysis population using descriptive statistics: number of participants with non-missing data (n), mean, SD, CV, median, minimum, maximum, geometric mean and geometric CV. All plasma PGRN concentration values that are BLQ will be set to ½ the lower limit of quantification (LLOQ) when calculating summary statistics.

Mean (±SD) absolute value, absolute change and percent change from baseline in plasma PGRN concentration versus nominal time profiles will be plotted on linear and semilogarithmic scales by cohort for the Full Analysis population. In addition, the absolute value, absolute change and percent change from baseline in plasma PGRN concentration at the individual level versus actual time profiles will be plotted on linear and semilogarithmic scales by cohort for the Full Analysis population.

8.2. Progranulin Cerebrospinal Fluid Samples

CSF samples will be evaluated for levels of PGRN. Cerebrospinal fluid samples will be collected in Part 1 only via lumbar puncture prior to study drug administration (if applicable) at Screening, Week 25, Week 49, and Week 97 (or the Part 1 EOT/EOS Visit) to evaluate PGRN.

The absolute value, absolute change, and percent change from baseline in CSF PGRN will be presented in data listings by cohort and timepoint for the Full Analysis population. CSF PGRN concentration data will be summarized by cohort and timepoint for the Full Analysis population using descriptive statistics: number of participants with non-missing data (n), mean, SD, CV, median, minimum, maximum, geometric mean and geometric CV. All CSF PGRN concentration values that are BLQ will be set to ½ the lower limit of quantification when calculating summary statistics.

Mean (±SD) absolute value, absolute change and percent change from baseline in CSF PGRN concentration versus nominal time profiles will be plotted on linear and semilogarithmic scales by cohort for the Full Analysis population. In addition, the absolute value, absolute change and

percent change from baseline in CSF PGRN concentration at the individual level versus actual time profiles will be plotted on linear and semilogarithmic scales by cohort for the Full Analysis population.

9. Exploratory Clinical outcome Assessments

All COAs will be collected at the timepoints identified in Appendix 14.1, Appendix 14.2, Appendix 14.4 and Appendix 14.5. The details of the COA are provided in Protocol Appendix 2.

Summaries of COA data will be provided using the Safety population. All COA data will be listed using the Enrolled population.

All COAs, except where indicated, will be assessed using MMRM methodology. The dependent variable will be the change from baseline to each postbaseline visit assessment. The fixed effect will include cohort, and time point will be the repeated measure. An interaction term for timepoint with cohort will be included. Covariates will not be explored due to small sample size. The MMRM will be constructed using unstructured covariance structure, however if the model will not converge AR(1) could be assessed . Estimates of the Least-squares mean, standard error, and 95% CI will be presented for each cohort and timepoint. The least-square means and 95% CI will be plotted by cohort and timepoint.

9.1. Analysis visit windows

The following analysis visit windows will be used for all COAs analyses:

Study day	Analysis Visit
Less or equal to 1	Baseline
Between 2 and 127	Week 13
Between 128 and 211	Week 25
Between 212 and 295	Week 37
Between 296 and 379	Week 49
Between 380 and 463	Week 61
Between 464 and 547	Week 73
Between 548 and 631	Week 85
Between 632 and 757	Week 97
Between 758 and 925	Week 121
Between 926 and 1093	Week 145
Between 1094 and 1275	Week 169
Greater than or equal to 1276	Week 197

9.2. Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Disease Coordinating Center Frontotemporal Lobar Degeneration Behavior and Language Domains (CDR® plus NACC FTLD)

The CDR® plus NACC FTLD results will be summarized by visit and domain. The Global Scores and individual domains will be summarized using the frequency count and percentage of participants in each result and the actual values and changes from baseline using descriptive statistics. The Sum of Boxes and Global Scores will be summarized for actual values and changes from baseline using descriptive statistics. Mean change from baseline, plus or minus the SD, will also be presented in a plot. Subject level data will be presented in a plot, grouped by cohort.

The Sum of Boxes will be assessed using the MMRM methodology described in Section 9.

9.3. Frontotemporal Dementia Rating Scale (FRS)

The FRS results will be summarized by visit and question. The question results will be summarized using the frequency count and percentage of participants in each response. The FRS Score, FRS Percentage Score, FRS Logit Score, and FRS Severity Category Score will be summarized for actual values and changes from baseline using descriptive statistics. Mean change from baseline, plus or minus the SD, will also be presented in a plot. Subject level data will be presented in a plot, grouped by cohort.

The FRS Score and FRS Percentage Score endpoints will be assessed using MMRM methodology described in Section 9.

9.4. Clinical Global Impression of Severity (CGI-S) and of Improvement (CGI-I)

The CGI-S and CGI-I results will be summarized by visit and question.

The question results will be summarized using the frequency count and percentage of participants in each response. In addition, the numeric score for each result will be summarized for actual values (both CGI-S and CGI-I) and changes from baseline (CGI-S only) using descriptive statistics. Mean (CGI-I), plus or minus the SD, will also be presented in a plot. Subject level data will be presented in a plot, grouped by cohort.

For the purposes of summarization using descriptive statistics and plots, the CGI-S Likert scores will equal character responses as follows: 1=Normal, not at all; 2=Borderline ill; 3=Mildly ill; 4=Moderately ill; 5=Markedly ill; 6=Severely ill; and 7=Among the most extremely ill.

For the purposes of summarization using descriptive statistics, and plots, the CGI-I Likert scores will be anchored to 0 as follows: -3=Very much worse; -2=Much Worse; -1=Minimally worse; 0=No change; 1=Minimally improved; 2=Much improved; 3=Very much improved.

9.5. Color Trails Test (CTT)

The CTT results will be summarized by visit and test. The question results will be summarized using the frequency count and percentage of participants in each response. The duration of the pretest and test will be summarized for actual values and changes from baseline using descriptive statistics. Mean change from baseline, plus or minus the SD, will also be presented in a plot. Subject level data will be presented in a plot, grouped by cohort.

In addition, CTT2 total time - CTT1 total time and CTT2 total time/CTT1 total time will be calculated and summarized.

The duration of test endpoint will be assessed using MMRM methodology described in Section 9.

9.6. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The RBANS results will be summarized by visit, domain, domain index score, and overall index score. The domain and overall index scores will be summarized for actual values and changes from baseline using descriptive statistics. Mean change from baseline, plus or minus the SD, will also be presented in a plot. Subject level data will be presented in a plot, grouped by cohort.

The index score endpoints will be assessed using MMRM methodology described in Section 9.

9.7. Neuropsychiatric Inventory (NPI), [redacted]; Part III), Delis-Kaplan Executive Function System (D-KEFS), and Interpersonal Reactivity Index (IRI)

The NPI, UPDRS, D-KEFS, and IRI were administered on participants enrolled under the original protocol dated 09 Apr 2019. The protocol amendment 1 dated 26 Sep 2019 did not include these assessments. Due to the limited availability of data from this change, the data from these assessments will not be summarized.

9.8. Optional Winterlight Labs Speech Assessments

The optional WLA will be analyzed and reported outside of this SAP.

10. Exploratory Pharmacodynamic Biomarkers

All analyses of exploratory PD biomarker data will be conducted using the Full analysis population.

10.1. Analysis visit windows

The following analysis visit windows will be used for all PD biomarker analyses:

Study day	Analysis Visit
Less or equal to 1	Baseline
Between 2 and 20	Week 2
Between 21 and 43	Week 5
Between 44 and 71	Week 9
Between 72 and 99	Week 13
Between 100 and 127	Week 17
Between 128 and 155	Week 21
Between 156 and 183	Week 25
Between 184 and 211	Week 29
Between 212 and 239	Week 33
Between 240 and 267	Week 37
Between 268 and 295	Week 41
Between 296 and 323	Week 45
Between 324 and 351	Week 49
Between 352 and 393	Week 53
Between 394 and 463	Week 61
Between 464 and 547	Week 73
Between 548 and 631	Week 85
Between 632 and 757	Week 97
Between 758 and 925	Week 121
Between 926 and 1093	Week 145
Between 1094 and 1275	Week 169
Greater than or equal to 1276	Week 197

All PD biomarker analyses will be conducted with one data point per time point and subject. If the measurement is available for the nominal time, its value will be used in the analyses. If the measurement for a nominal time point is missing and measurements for unscheduled visits that fall in the corresponding analysis window are available, the value from the sample collected closest to the nominal time point will be used.

10.2. Exploratory Pharmacodynamic Biomarkers of Neurodegeneration, lysosomal function, and glial activity

Exploratory plasma and CSF PD biomarker samples are collected for evaluation for neurodegeneration (e.g., neurofilament-light chain [NfL]), lysosomal function (e.g., cathepsins), and glial activity (e.g., YKL 40, GFAP), and to potentially evaluate levels of other analytes relevant to disease biology and response to AL001. CSF PD biomarker samples are collected in Part 1 only. The timepoint at which the exploratory PD biomarkers of neurodegeneration are identified in Appendix 14.1, Appendix 14.2, Appendix 14.4 and Appendix 14.5.

For all biomarkers listed in the following table, the absolute value, absolute change, percent change from baseline, and ratio to baseline values for exploratory biomarker parameters will be summarized by visit and cohort using descriptive statistics, including the number of participants, mean, SD, median, min and max. Additionally, for absolute value and ratio to baseline, geometric mean (calculated as exp (mean(log(absolute value or ratio to baseline)))) and geometric SD will be summarized. For NfL and GFAP, mean absolute value, mean percent change from baseline values, and geometric mean ratio to baseline plus or minus the SD, will also be plotted versus nominal time points up to Week 49. All biomarker concentration values that are BLQ will be set to ½ of LLOQ when calculating summary statistics. In the case of Vendor not providing LLOQ, such as Cell Carta, data points with results being 0 will be excluded from the analysis.

Exploratory Pharmacodynamic Biomarkers		
C1Qb	[redacted]	[redacted]
C1Qc	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	YKL40
CTSD	LAMP1	[redacted]
[redacted]	[redacted]	MIF
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	GFAP
[redacted]	[redacted]	[redacted]

- For the GFAP analysis, only GFAP data from Quanterix will be used. Data on CSF GFAP initially obtained on the Roche NTK platform will be excluded from the data analysis, as those samples were subsequently re-analyzed on the Quanterix SIMOA platform. At the time of analysis, Roche did not have the capability to analyze plasma samples for GFAP. Since plasma GFAP was analyzed on the Quanterix platform, all GFAP (plasma and CSF) analyses were ultimately conducted on the Quanterix platform in order to maintain consistency between matrices.

- For the biomarker data obtained from Cell Carta, each biomarker was assayed with 7 different peptides. The analysis will only include data from the peptide recommended by the Vendor for each biomarker for analysis. The list of recommended peptides is shown in the following table:

Protein	[redacted]
C1qB	C1QB_HUMAN_IAFSATR_y4+
C1qC	C1QC_HUMAN_FQSVFTVTR_b2+
[redacted]	
[redacted]	
CTSD	CATD_HUMAN_VSTLPAITLK_y7+
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
LAMP1	LAMP1_HUMAN_AFSVNIFK_y6+
[redacted]	
[redacted]	
[redacted]	

- Participants who have completed Study AL001-1 and who enrolled in this study may not have had a CSF collection at screening in this study if the baseline LP was performed in the AL001-1 study within 3 months prior to screening into AL001-2. For those participants, the baseline values for certain CSF biomarkers will be obtained from the data in the AL001-1 study.

10.3. Brain Imaging

Brain imaging including structural MRI and DTI assessments will be performed at the timepoints indicated in Appendix 14.1, Appendix 14.2, Appendix 14.4 and Appendix 14.5.

Brain imaging measurements include:

- Regional brain volumes as measured by MRI
- Diffusion fractional anisotropy (FA) in Corpus Callosum only as measured by DTI

Actual results and percent change from baseline values for quantitative MRI (frontotemporal, parietal, and subcortical regions only) and FA parameters will be summarized by visit using descriptive statistics. Mean and median percent change from baseline values, the standard deviation, minimum and maximum will also be presented in a plot.

All MRI and DTI data will be presented in data listings.

10.4. Exploratory Correlation Analyses

Exploratory correlation analysis will be conducted between selected biomarkers (PGRN, NfL and GFAP) and CDR® plus NACC FTLD Sum of Boxes (FTLD-CDR-SB), for samples collected from both plasma and CSF with baseline and at least one post-baseline measurement in the full analysis population. Summary tables will be provided to show the relationship between each fluid PD biomarker and FTLD-CDR-SB by cohort. The summary tables will include the total number of data points, as well as the Pearson and Spearman correlation coefficients. Scatter plots of actual values for fluid PD biomarkers as the X-axis variable and FTLD-CDR-SB scores as the Y-axis variable will be plotted and will include the Pearson and Spearman correlation coefficients from the summary tables.

A similar but separate analysis to assess the correlations among selected fluid PD biomarker (NfL and GFAP only) levels and quantitative brain imaging parameters MRI (frontotemporal, parietal, and subcortical regions only) will be performed.

Additionally, for the selected fluid biomarkers, the absolute change from baseline to week 49 and percent change over the same interval will be correlated against the absolute change in FTLD-CDR-SB. For selected regional volumetrics (i.e., frontotemporal, parietal, and subcortical regions), the percent change from baseline to week 49 will be correlated with FTLD-CDR-SB scores. The results will be presented in summary tables and scatter plots as described above. Only subjects with both baseline and week-49 biomarker and FTLD-CDR-SB data in the full analysis population will be included.

11. Interim Analysis

No interim analyses are planned for this study.

An iDMC will review safety data during the course of the study to provide recommendations to Alector on study conduct. The details of the iDMC are provided in a separate charter.

12. Changes in the Planned Analysis

Physical and neurological examinations will not be summarized or listed since exam results are only entered on the General Medical History and Baseline Conditions or AE pages of the eCRF.

Due to the high rate of participant attrition over the study duration and small FTD cohort sizes, time points beyond Week 49 will not be included in the cohort level summary of the figures.

Apolipoprotein-B100 samples will not be analyzed (or summarized/listed) due to vendor discontinuation of the assay. Standard lipid analytes are evaluated for safety (Cholesterol, HDL, LDL, Triglycerides) and will be reported as summarized in Section 8.2.

WBC samples for analysis for Sortilin expression were collected to serve as a pharmacodynamic biomarker of target engagement. Development of this assay found that stability of these samples was not reliable for accurate measurement. Expression of PGRN levels in the plasma and CSF will be used as a biomarker of target engagement, and will be reported as summarized in Section 10.

The following exploratory MRI analyses listed in the protocol will not be performed due to evidence from the literature that these are unlikely to change over the duration of participation in this trial: global brain volume; white matter hyperintensities; brain perfusion as measured by arterial spin labeling; and mean, axial and radial diffusivity as measured by diffusion tensor imaging. Other MRI analyses (including safety assessments) will be reported as summarized in Sections 8.8 and 12.2.

13. References

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14. Appendices

14.1. Schedule of Assessments for Part 1, Treatment Period (Through Week 53)

Procedures[m]	Screening	Treatment Period														
Visits		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Study week	**-6**	**1**	**2**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**53**
Study day		**1**	**10**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**
Visit window (days)	**42 Total**	**0**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Informed consent	x															
Demographics[a]	x															
Medical history review	x	x														
Physical examination[b]	x[b]	x	x	x	x	x	x	x	x[b]	x	x	x	x	x	x[b]	X
Neurological examination[c]	x[c]	x		x	x	x	x	x	x[c]	x	x	x	x	x	x[c]	x
Vital signs and weight[d,f]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG[e,f]	x	x							x						x	
Clinical chemistry, hematology[g]	x	x		x	x	x			x			x			x	
Coagulation[g,h]	x							x						x		
Urinalysis[g]	x	x				x			x			x			x	
Serology[g,i]	x															
Pregnancy test[g,j]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Serum PK samples[f,g,k]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PGRN Plasma samples[f,g]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Whole blood for WBC[f,g]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Whole blood for WGS	x															
Serum ADA samples[f,g,k]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Exploratory plasma PD biomarker samples[f,g]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Procedures[m]	Screening	Treatment Period														
Visits		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Study week	**-6**	**1**	**2**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**53**
Study day		**1**	**10**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**
Visit window (days)	**42 Total**	**0**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Exploratory whole blood PD biomarker samples [f,g]		x	x			x			x			x			x	
Lumbar puncture/CSF[l]	x								x						x	
Brain MRI[n]	x								x						x	
Diagnostic characterization[o]	x															
COAs[p]	x					x			x			x			x	
Winterlight-A Lab Speech Assessment (Optional)[q]		x				x			x			x			x	
Winterlight-B Lab Speech Assessment (Optional)[q]		x		x	x		x	x		x	x		x	x		x
Review of AEs and concomitant medications[r]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Sheehan-STS	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study drug administration		x		x	x	x	x	x	x	x	x	x	x	x	x	x

Abbreviations: ADA, anti-drug antibody; AE, adverse event; CGI-I, Clinical Global Impression of Improvement; COA, clinical outcome assessment; CSF, cerebrospinal fluid; ECG, electrocardiogram; eCRF, electronic case report form; IL-6, Interleukin 6; MRI, magnetic resonance imaging; PD, pharmacodynamic; PE, physical examination; PGRN, progranulin; PK, pharmacokinetic; Sheehan-STS, Sheehan Suicidality Tracking Scale; V, visit; WBC, white blood cell; WGS, whole genome sequencing.

a Demographic information (year of birth, age, sex, race, ethnicity) will be recorded at screening, unless disallowed by local regulatory agencies.

b A complete PE will be performed at screening, Week 25, Week 49, Week 73, Week 97 and at EOT/EOS/Safety Follow-up, and includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory and gastrointestinal systems. Breast, genital, and rectal examinations are not required, unless warranted in opinion of the health care provider. The examination will be performed by a physician, or a nurse practitioner or physician's assistant under the supervision of a physician. Limited or symptom-directed examinations is required at all other specified time points, prior to study drug administration (if applicable). A limited examination or symptom-directed examination should focus on the affected organ system or body area. Record abnormalities observed at screening on the General Medical History and Baseline Conditions page of the eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the AE eCRF. Height (cm) will be measured at screening.

c A complete neurological examination will be performed at screening, Week 25, Week 49, Week 73, Week 97 and at EOT/EOS/Safety Follow-up, and includes the evaluation of consciousness, orientation, cranial nerves, motor and sensory system, coordination and gait, and reflexes. Limited or symptom directed examinations are required at all other specified time points, prior to study drug administration (if applicable). A limited examination or symptom directed examination should focus on the organ system or affected body area. Record abnormalities observed at screening on the General Medical History and Baseline Conditions page of the eCRF. At subsequent visits, record new or worsened clinically significant abnormalities as AEs on the AE eCRF.

d Vital signs will be recorded after the participant has been resting for at least 5 minutes in the supine position. On dosing days, vital signs will be recorded prior to infusion (pre-dose) and within 15 minutes after the end of infusion, and once at all other specified time points as indicated. Weight (kg) will be collected at the same visits that vital signs are taken.

e Triplicate 12-lead ECGs will be obtained after the participant has been in the supine position for $\geqslant$5 minutes. On specified dosing days ECG will be obtained prior to study drug administration and within 60 minutes after the end of infusion, and once at all other specified time points as indicated. Additional ECG monitoring must be performed during the treatment period if clinically indicated.

f Details on timing of vital signs, serum PK samples, triplicate ECGs, serum ADA samples, progranulin plasma samples, exploratory plasma PD biomarker samples, whole blood samples for WBC analysis, and exploratory whole blood PD biomarker samples are provided in protocol Table 6.

g Samples will be collected prior to study drug administration (if applicable).

h If the lumbar puncture is moved to a different visit, the coagulation panel will be moved to the visit immediately preceding the new lumbar puncture visit.

i Serology testing will include anti-HCV, anti-HIV, HIV antigen, HBsAg, and total hepatitis B core antibody.

j All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

k Blood serum samples will be collected for determination of ADA prior to study drug administration (if applicable). Additional ADA samples should be collected in participants with signs and symptoms of infusion-related reactions. A sample of blood should be obtained for PK serum and ADA assessment of AL001, and testing should be performed for C-reactive protein, tryptase, and Interleukin 6 (IL-6).

l Cerebrospinal fluid samples will be collected via lumbar puncture prior to study drug administration (if applicable). The timing of lumbar punctures may be adjusted as determined by Alector's review of exploratory PD biomarkers. *GRN* mutation carriers previously treated in Study AL001-1 may not be required to repeat the CSF assessment if it has been performed within 3 months prior to screening.

m If the assessment is unable to be performed at the scheduled visit due to the COVID-19 pandemic, the assessments may be performed at a future on-site visit with approval from the medical monitor. Refer to protocol Appendix 3 for additional details on trial adaptations due to COVID-19.
n During study drug treatment, magnetic resonance imaging to be performed within ±7 days of a treatment visit. *GRN* mutation carriers previously treated in Study AL001-1 may not be required to repeat the imaging screening assessment if it has been performed within 3 months prior to screening.
o A diagnostic characterization form will be completed in an electronic data capture system at screening, week 97, and EOT/EOS for symptomatic participants only. It will also be completed for any asymptomatic participant who becomes symptomatic during the course of the study; for these participants, the diagnostic characterization form will be completed only at the first visit in which they exhibit clinical symptomatology.
p The COAs consist of the Clinical Dementia Rating Scale plus behavior and language domains from the National Alzheimer's Disease Coordinating Center Frontotemporal Lobar Degeneration module, Frontotemporal Dementia Rating Scale, Clinical Global Impression of Improvement, Clinical Global Impression of Severity, Color Trails Test Part 2, and the Repeatable Battery for the Assessment of Neuropsychological Status. The Clinical Global Impression of Improvement is not administered at baseline. Neurocognitive and functional tests will be performed prior to study drug administration (if applicable) and prior to any stressful procedures (e.g., blood collections, imaging).
q Winterlight Labs Speech Assessments (WLA) (for US, UK, and Canadian participants who agree to participate in the optional assessments only) will be conducted at home. Participants will have the option to complete the WLA after assessment visits only (WLA-A), after treatment visits only (WLA-B) or both (WLA-A and WLA-B). Assessments are conducted at home within ±7 days of the visit and will be supervised by the study partner. The study partner will be asked to complete a questionnaire online within ±7 days of the EOS visit.
r All AEs and SAEs must be recorded and reported, regardless of cause or relationship, that occur after the participant signs informed consent and through the Part1/Part 2 EOS or Safety Follow-up visit, whichever is later. Any unresolved AEs and SAEs will be followed up through satisfactory clinical resolution. Additionally, SAEs considered related to study drug which occur at any time during the study will be reported by the investigator regardless of the AE/SAE collection window. At every study visit, participants will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (prescription drugs, herbal products, vitamins, minerals, vaccines, topical medications, and over-the-counter medications). Review of AEs and concomitant medications will be performed before and after study drug administration (when applicable).

14.2. Appendices Schedule of Assessments for Part 1, Treatment Period (Through Week 97)

Procedures[m]	**Treatment Period (continued)**												**Part 1 EOT/EOS[s,t]**	**Safety Follow-up[b,s]**
Visits	**V16**	**V17**	**V17A[a]**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26[s]**		
Study week	**57**	**61**	**61**	**65**	**69**	**73**	**77**	**81**	**85**	**89**	**93**	**97[b]**		
Study day	**393**	**421**	**422**	**449**	**477**	**505**	**533**	**561**	**589**	**617**	**645**	**673**		
Visit window (days)	±7	±7	±7[a]	±7	±7	±7	±7	±7	±7	±7	±7	±7		±7
Physical examination[c]	x	x		x	x	x[c]	x	x	x	x	x	x[c]	x[c]	x[c]
Neurological examination[d]	x	x		x	x	x[d]	x	x	x	x	x	x[d]	x[d]	x[d]
Vital signs and weight[e,g]	x	x		x	x	x	x	x	x	x	x	x	x	x
ECG[f,g]						x						x	x	x
Clinical chemistry, hematology[h]		x				x			x			x	x	x
Coagulation[h,i]						x					x			
Urinalysis[h]		x				x			x			x	x	x
Pregnancy test[h,j]	x	x		x	x	x	x	x	x	x	x	x	x	x
Serum PK samples[g,h,k]		x	x			x			x			x	x	x
PGRN Plasma samples[g,h]		x	x			x			x			x	x	x
Whole blood for WBC[g,h]		x				x			x			x	x	
Serum ADA samples[g,h,k]		x				x			x			x	x	x
Exploratory plasma PD biomarker samples[g,h]		x				x			x			x	x	
Exploratory whole blood PD biomarker samples[g,h]		x				x			x			x	x	
Lumbar puncture/CSF[l]												x	x	
Brain MRI[n]						x						x	x	
Diagnostic characterization[o]												x	x	
COAs[p]		x				x			x			x	x	
Winterlight-A Lab Speech Assessment (Optional)[q]		x				x			x			x	x	
Winterlight-B Lab Speech Assessment (Optional)[q]	x			x	x		x	x		x	x			
Review of AEs and concomitant medications[r]	x	x		x	x	x	x	x	x	x	x	x	x	x
Sheehan-STS	x	x		x	x	x	x	x	x	x	x	x	x	x
Study drug administration	x	x		x	x	x	x	x	x	x	x	x		

Abbreviations: ADA, anti-drug antibody; AE, adverse event; CGI-I, Clinical Global Impression of Improvement; COA, clinical outcome assessment; CSF, cerebrospinal fluid; ECG, electrocardiogram; eCRF, electronic case report form; EOS, End of Study; EOT, End of Treatment; IL-6, Interleukin 6; MRI, magnetic resonance imaging; PD, pharmacodynamic; PE, physical examination; PGRN, progranulin; PK, pharmacokinetic; Sheehan-STS, Sheehan Suicidality Tracking Scale; V, visit; WBC, white blood cell; WGS, whole genome sequencing.
a Visit 17A should occur the following day after Visit 17.
b A Safety Follow-up visit will be performed 10 weeks following the last dose of AL001. The Safety Follow-up visit may be substituted by a scheduled visit if it occurs within the same window.
c A complete PE will be performed at screening, Week 25, Week 49, Week 73, Week 97 and at EOT/EOS/Safety Follow-up, and includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory and gastrointestinal systems. Breast, genital, and rectal examinations are not required, unless warranted in opinion of the health care provider. The examination will be performed by a physician, or a nurse practitioner or physician's assistant under the supervision of a physician. Limited or symptom-directed examination are required at all other specified time points, prior to study drug administration (if applicable). A limited examination or symptom-directed examination should focus on the organ system or affected body area. Record abnormalities observed at screening on the General Medical History and Baseline Conditions page of the eCRF. Height (cm) will be measured at screening. At subsequent visits, record new or worsened clinically significant abnormalities on the AE eCRF.
d A complete neurological examination will be performed at screening, Week 25, Week 49, Week 73, Week 97 and at EOT/EOS/Safety Follow-up, and includes the evaluation of consciousness, orientation, cranial nerves, motor and sensory system, coordination and gait, and reflexes. Limited or symptomdirected examinations are required at all other specified time points, prior to study drug administration (if applicable). A limited examination or symptomdirected examination should focus on the affected organ system or body area. Record abnormalities observed at screening on the General Medical History and Baseline Conditions page of the eCRF. At subsequent visits, record new or worsened clinically significant abnormalities as AEs on the AE eCRF.
e Vital signs will be recorded after the participant has been resting for at least 5 minutes in the supine position. On dosing days, vital signs will be recorded prior to infusion (pre-dose) and within 15 minutes after the end of infusion, and once at all other specified time points as indicated. Weight (kg) will be collected at the same visits that vital signs are taken.
f Triplicate 12-lead ECGs will be obtained after the participant has been in the supine position for ⩾5 minutes. On specified dosing days ECG will be obtained prior to study drug administration and within 60 minutes after the end of infusion, and once at all other specified time points as indicated. Additional ECG monitoring must be performed during the treatment period if clinically indicated.
g Details on timing of vital signs, serum PK samples, triplicate ECGs, serum ADA samples, progranulin plasma samples, exploratory plasma PD biomarker samples, whole blood samples for WBC analysis, and exploratory whole blood PD biomarker samples are provided in protocol Table 6.
H Samples will be collected prior to study drug administration (if applicable).
I If the lumbar puncture is moved to a different visit, the coagulation panel will be moved to the visit immediately preceding the new lumbar puncture visit.
J All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
K Blood serum samples will be collected for determination of ADA prior to study drug administration (if applicable). Additional ADA samples should be collected in participants with signs and symptoms of infusion-related reactions. A sample of blood should be obtained for PK serum and ADA assessment of AL001, and testing should be performed for C-reactive protein, tryptase, and Interleukin 6 (IL-6).
L Cerebrospinal fluid samples will be collected via lumbar puncture prior to study drug administration (if applicable). The timing of lumbar puncture may be adjusted as determined by Alector's review of exploratory PD biomarkers. *GRN* mutation carriers previously treated in Study AL001-1 may not be required to repeat the CSF assessment if it has been performed within 3 months prior to screening.

M If the assessment is unable to be performed at the scheduled visit due to the COVID-19 pandemic, the assessments may be performed at a future on-site visit with approval from the medical monitor. Refer to protocol Appendix 3 for additional details on trial adaptations due to COVID-19.
n During study drug treatment, magnetic resonance imaging to be performed within ±7 days of a treatment visit. *GRN* mutation carriers previously treated in Study AL001-1 may not be required to repeat the imaging screening assessment if it has been performed within 3 months prior to screening.
o A diagnostic characterization form will be completed in an electronic data capture system at screening, week 97, and EOT/EOS for symptomatic participants only. It will also be completed for any asymptomatic participant who becomes symptomatic during the course of the study; for these participants, the diagnostic characterization form will be completed only at the first visit in which they exhibit clinical symptomatology.
p The COAs consist of the Clinical Dementia Rating Scale plus behavior and language domains from the National Alzheimer's Disease Coordinating Center Frontotemporal Lobar Degeneration module, Frontotemporal Dementia Rating Scale, Clinical Global Impression of Improvement, Clinical Global Impression of Severity, Color Trails Test Part 2, and the Repeatable Battery for the Assessment of Neuropsychological Status. The Clinical Global Impression of Improvement is not administered at baseline. Neurocognitive and functional tests will be performed prior to study drug administration (if applicable) and prior to any stressful procedures (e.g., blood collections, imaging).
q Winterlight Labs Speech Assessments (WLA) (for US, UK, and Canadian participants who agree to participate in the optional assessments only) will be conducted at home. Participants will have the option to complete the WLA after assessment visits only (WLA-A), after treatment visits only (WLA-B) or both (WLA-A and WLA-B). Assessments are conducted at home within +/- 7 days of the visit and will be supervised by the study partner. The study partner will be asked to complete a questionnaire online within +/- 7 days of the Study Completion visit.
r All AEs and SAEs must be recorded and reported, regardless of cause or relationship, that occur after the participant signs informed consent and through the Part 1/Part 2 EOS or Safety Follow-up visit, whichever is later. Any unresolved AEs and SAEs will be followed up through satisfactory clinical resolution. Additionally, SAEs considered related to study drug which occur at any time during the study will be reported by the investigator regardless of the AE/SAE collection window. At every study visit, participants will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (prescription drugs, herbal products, vitamins, minerals, vaccines, topical medications, and over-the-counter medications). Review of AEs and concomitant medications will be performed before and after study drug administration (when applicable).
s Participants who complete the Part 1 96-week treatment period (Week 97), who provide informed consent to participate in Part 2 (optional OLE) and meet all the eligibility criteria for the Part 2 OLE (prior to Week 101 study drug administration), will complete the Week 97 visit and continue to Part 2 (Week 101) to receive their next regularly scheduled dose of AL001 according to the OLE administration schedule (continuation from Week 97 to Week 101). All other participants who complete the Part 1 96-week treatment period and who do not continue in Part 2 will complete a Part 1 EOS visit at the scheduled Week 97 timepoint. A Safety Follow-up visit will be performed 10-weeks after their last study drug administration (Week 107, +/- 7 days).
t A Part 1 EOT visit will be completed by participants who discontinue study drug but remain in the study and continue to perform assessments. Part 1 EOT assessments should be completed as soon as possible after the decision is made. A Part 1 EOS visit will be completed by participants who discontinue study drug and all assessments. Part 1 EOS assessments should be completed as soon as possible after the decision is made.

14.3. Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarker Sample and Imaging Assessments – Part 1, Treatment Period

Timepoint	Vital Signs	Serum PK sample [a]	Triplicate ECG	Serum ADA sample	Progranulin plasma sample	Exploratory plasma PD biomarker samples [b]	Whole blood for WBC	Exploratory whole blood PD biomarker samples [c]
Screening	x		x					
V1 (Week 1): Predose	x	x	x	x	x	x	x	x
V1 (Week 1): End of infusion	x	x	x					
V2 (Week 2)	x	x		x	x	x	x	x
V3 (Week 5): Predose	x	x			x	x	x	
V3 (Week 5): End of infusion	x	x						
V4 (Week 9): Predose	x	x			x	x	x	
V4 (Week 9): End of infusion	x	x						
V5 (Week 13): Predose	x	x		x	x	x	x	x
V5 (Week 13): End of infusion	x	x						
V6 (Week 17): Predose	x	x			x	x	x	
V6 (Week 17): End of infusion	x	x						
V7 (Week 21): Predose	x	x			x	x	x	
V7 (Week 21): End of infusion	x	x						
V8 (Week 25): Predose	x	x	x	x	x	x	x	x
V8 (Week 25): End of infusion	x	x	x					
V9 (Week 29): Predose	x	x			x	x	x	
V9 (Week 29): End of infusion	x	x						
V10 (Week 33): Predose	x	x			x	x	x	
V10 (Week 33): End of infusion	x	x						
V11 (Week 37): Predose	x	x		x	x	x	x	x
V11 (Week 37): End of infusion	x	x						
V12 (Week 41): Predose	x	x			x	x	x	
V12 (Week 41): End of infusion	x	x						
V13 (Week 45): Predose	x	x			x	x	x	
V13 (Week 45): End of infusion	x	x						
V14 (Week 49): Predose	x	x	x	x	x	x	x	x
V14 (Week 49): End of infusion	x	x	x					
V15 (Week 53): Predose	x	x		x	x	x	x	
V15 (Week 53): End of infusion	x	x						
V16 (Week 57): Predose	x							

Timepoint	Vital Signs	Serum PK sample [a]	Triplicate ECG	Serum ADA sample	Progranulin plasma sample	Exploratory plasma PD biomarker samples [b]	Whole blood for WBC	Exploratory whole blood PD biomarker samples [c]
V16 (Week 57): End of infusion	x							
V17 (Week 61): Predose	x	x						
V17 (Week 61): End of infusion	x	x		x	x	x	x	x
V17 (Week 61): 3 hr ± 90 minutes post end of infusion		x						
V17A (Week 61): The next day after V17		x			x			
V18 (Week 65): Predose	x							
V18 (Week 65): End of infusion	x							
V19 (Week 69): Predose	x							
V19 (Week 69): End of infusion	x							
V20 (Week 73): Predose	x	x	x	x	x	x	x	x
V20 (Week 73): End of infusion	x	x	x					
V21 (Week 77): Predose	x							
V21 (Week 77): End of infusion	x							
V22 (Week 81): Predose	x							
V22 (Week 81): End of infusion	x							
V23 (Week 85): Predose	x	x		x	x	x	x	x
V23 (Week 85): End of infusion	x	x						
V24 (Week 89): Predose	x							
V24 (Week 89): End of infusion	x							
V25 (Week 93): Predose	x							
V25 (Week 93): End of infusion	x							
V26 (Week 97): Predose	x	x	x	x	x	x	x	x
V26 (Week 97): End of infusion	x	x	x					
Safety Follow-up	x	x	x	x	x			
Part 1 EOT/EOS	x	x	x	x	x	x	x	x

Abbreviations: ADA, anti-drug antibody; ECG, electrocardiogram; EOS, End of Study; EOT, End of Treatment; hr, hour; PD, pharmacodynamic; PK,:pharmacokinetic; V, visit; WBC, white blood cell.

a The window for serum PK samples is within 15 minutes after the end of the infusion.

b Exploratory PD biomarkers include Neurofilament Light chain, [redacted] in plasma and other analytes.

c Exploratory whole blood biomarkers include mRNA and other analytes.

14.4. Schedule of Assessments for Part 2 (Optional OLE) (Through Week 161)

Procedures[j]	**OLE Part 2 Treatment Period**															
Visits	**V27[a]**	**V28**	**V29**	**V30**	**V31**	**V32**	**V33**	**V34**	**V35**	**V36**	**V37**	**V38**	**V39**	**V40**	**V41**	**V42**
Study week	**101**	**105**	**109**	**113**	**117**	**121**	**125**	**129**	**133**	**137**	**141**	**145**	**149**	**153**	**157**	**161**
Study day	**701**	**729**	**757**	**785**	**813**	**841**	**869**	**897**	**925**	**953**	**981**	**1009**	**1037**	**1065**	**1093**	**1121**
Visit window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Informed Consent[a]	x															
Physical examination[b]						x[b]						x[b]				
Neurological examination[c]						x[c]						x[c]				
Vital signs and weight[d,f]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG[e,f]						x						x				
Clinical chemistry, hematology[g]			x			x			x			x			x	
Urinalysis[g]						x						x				
Pregnancy test[g,h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum PK samples[f,g,i]						x						x				
PGRN Plasma samples[f,g]						x						x				
Serum ADA samples[f,g,i]						x						x				
Exploratory plasma PD biomarker samples [f,g]						x						x				
Brain MRI[k]												x				
Diagnostic characterization[l]																
COAs[m]						x						x				
Winterlight-A Labs Speech Assessment (Optional)[n]			x			x			x			x			x	
Winterlight-B Labs Speech Assessment (Optional)[n]	x	x		x	x		x	x		x	x		x	x		x

Review of AEs and concomitant medications[o]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Sheehan-STS	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study drug administration	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Abbreviations: ADA, anti-drug antibody; AE, adverse event; CGI-I, Clinical Global Impression of Improvement; COA, clinical outcome assessment; ECG, electrocardiogram; eCRF, electronic case report form; IL-6, Interleukin 6; MRI, magnetic resonance imaging; PD, pharmacodynamic; PE, physical examination; PGRN, progranulin; PK, pharmacokinetic; Sheehan-STS, Sheehan Suicidality Tracking Scale; V, visit.

a There is no Screening period for participants that opt-in to continue receiving AL001 in Part 2 (Optional OLE) of the study. Participants who complete the Part 1 96-week treatment period (Week 97), who provide informed consent to participate in Part 2 (optional OLE) and meet all the eligibility criteria for the Part 2 OLE (prior to Week 101 study drug administration), will complete the Week 97 visit and continue to Part 2 (Week 101) to receive their next regularly scheduled dose of AL001 according to the OLE administration schedule (continuation from Week 97 to Week 101). Visit 27/Week 101 of Part 2 (Optional OLE) will be conducted 4 weeks after Visit 26/Week 97 of the Part 1 Treatment Period for those participants who are eligible to participate.

b A complete PE will be performed at Week 121, Week 145, Week 169, Week 197 and at EOS/Safety Follow-up, and includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory and gastrointestinal systems. Breast, genital, and rectal examinations are not required, unless warranted in opinion of the health care provider. The examination will be performed by a physician, or a nurse practitioner or physician's assistant under the supervision of a physician. If applicable, limited or symptom-directed examinations will be performed at all other specified time points, prior to study drug administration. A limited examination or symptom-directed examination should focus on the affected organ system or body area. Record new or worsened clinically significant abnormalities on the AE eCRF. Height (cm) does not need to be collected in Part 2 OLE.

c A complete neurological examination will be performed at Week 121, Week 145, Week 169, Week 197 and at EOS/Safety Follow-up, and includes the evaluation of consciousness, orientation, cranial nerves, motor and sensory system, coordination and gait, and reflexes. If applicable, limited or symptomdirected examinations will be performed at all other specified time points, prior to study drug administration. A limited examination or symptom-directed examination should focus on the organ system or affected body area. Record new or worsened clinically significant abnormalities as AEs on the AE eCRF.

d Vital signs will be recorded after the participant has been resting for at least 5 minutes in the supine position. On dosing days, vital signs will be recorded prior to infusion (pre-dose) and within 15 minutes after the end of infusion, and once at all other specified time points as indicated. Weight (kg) will be collected at the same visits that vital signs are taken.

e Triplicate 12-lead ECGs will be obtained after the participant has been in the supine position for $\geqslant$5 minutes. On specified dosing days, ECG will be obtained prior to study drug administration and within 60 minutes after the end of the infusion, and once at all other specified time points as indicated. Additional ECG monitoring must be performed during treatment period if clinically indicated.

f Details on timing of vital signs, serum PK samples, triplicate ECGs, serum ADA samples, progranulin plasma samples, and exploratory plasma PD biomarker samples, are provided in protocol Table 9.

g Samples will be collected prior to study drug administration (if applicable).

h All women of childbearing potential will have urine pregnancy tests at specified visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

i Blood serum samples will be collected for determination of ADA prior to study drug administration (if applicable). Additional ADA samples should be collected in participants with signs and symptoms of infusion-related reactions. A sample of blood should be obtained for PK serum and ADA assessment of AL001, and testing should be performed for C-reactive protein, tryptase, and Interleukin 6 (IL-6).

j If the assessment is unable to be performed at the scheduled visit due to the COVID-19 pandemic, the assessments may be performed at a future on-site visit with approval from the medical monitor. Refer to protocol Appendix 3 for additional details on trial adaptations due to COVID-19.
k During study drug treatment, magnetic resonance imaging to be performed within ±7 days of a treatment visit.

l A diagnostic characterization form will be completed for symptomatic patients at Week 197/Part 2 EOS. It will also be completed for any asymptomatic participant who becomes symptomatic during the course of the study; for these participants, the diagnostic characterization form will be completed only at the first visit in which they exhibit clinical symptomatology.
m The COAs consist of the Clinical Dementia Rating Scale plus behavior and language domains from the National Alzheimer's Disease Coordinating Center Frontotemporal Lobar Degeneration module, Frontotemporal Dementia Rating Scale, Clinical Global Impression of Improvement, Clinical Global Impression of Severity, Color Trails Test Part 2, and the Repeatable Battery for the Assessment of Neuropsychological Status. Neurocognitive and functional tests will be performed prior to study drug administration (if applicable) and prior to any stressful procedures (e.g., blood collections, imaging).
n Winterlight Labs Speech Assessments (WLA) (for US, UK, and Canadian participants who agree to participate in the optional assessments only) will be conducted at home. Participants will have the option to complete the WLA after assessment visits only (WLA-A), after treatment visits only (WLA-B) or both (WLA-A and WLA-B). Assessments are conducted at home within ±7 days of the visit and will be supervised by the study partner. The study partner will be asked to complete a questionnaire online within ±7 days of the EOS visit.
o All AEs and SAEs must be recorded and reported, regardless of cause or relationship, that occur after the participant signs informed consent and through the Part1/Part2 EOS or Safety Follow-up visit, whichever is later. Any unresolved AEs and SAEs will be followed up through satisfactory clinical resolution. Additionally, SAEs considered related to study drug which occur at any time during the study will be reported by the investigator regardless of the AE/SAE collection window. At every study visit, participants will be asked a standard non-leading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (prescription drugs, herbal products, vitamins, minerals, vaccines, topical medications, and over-the-counter medications). Review of AEs and concomitant medications will be performed before and after study drug administration (when applicable).

14.5. Schedule of Assessments for Part 2 (Optional OLE) (Through Week 197)

Procedures[i]	OLE Part 2 Treatment Period (continued)									Part 2 EOS[o,p]	Safety Follow-up[q]
Visits	**V43**	**V44**	**V45**	**V46**	**V47**	**V48**	**V49**	**V50**	**V51°**		
Study week	**165**	**169**	**173**	**177**	**181**	**185**	**189**	**193**	**197**		
Study day	**1149**	**1177**	**1205**	**1233**	**1261**	**1289**	**1317**	**1345**	**1373**		
Visit window (days)	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		**±7**
Physical examination[a]		x[a]							x[a]	x[a]	x[a]
Neurological examination[b]		x[b]							x[b]	x[b]	x[b]
Vital signs and weight[c,e]	x	x	x	x	x	x	x	x	x	x	x
ECG[d,e]		x							x	x	x
Clinical chemistry, hematology[f]		x			x				x	x	x
Urinalysis[f]		x							x	x	x
Pregnancy test[f,g]	x	x	x	x	x	x	x	x	x	x	x
Serum PK samples[e,f,h]		x							x	x	x
PGRN Plasma samples[e,f]		x							x	x	x
Serum ADA samples[e,f,h]		x							x	x	x
Exploratory plasma PD biomarker samples[e,f]		x							x	x	
Brain MRI[j]									x	x	
Diagnostic characterization[k]									x	x	
COAs[l]		x							x	x	
Winterlight-A Labs Speech Assessment (Optional)[m]		x			x				x	x	
Winterlight-B Labs Speech Assessment (Optional)[m]	x		x	x		x	x	x			
Review of AEs and concomitant medications[n]	x	x	x	x	x	x	x	x	x	x	x
Sheehan-STS	x	x	x	x	x	x	x	x	x		x
Study drug administration	x	x	x	x	x	x	x	x	x		

Abbreviations: ADA, anti-drug antibody; AE, adverse event; CGI-I, Clinical Global Impression of Improvement; COA, clinical outcome assessment; ECG, electrocardiogram; eCRF, electronic case report form; IL-6, Interleukin 6; MRI, magnetic resonance imaging; PD, pharmacodynamic; PE, physical examination; PGRN, progranulin; PK, pharmacokinetic; Sheehan-STS, Sheehan Suicidality Tracking Scale; V, visit.

a A complete PE will be performed at Week 121, Week 145, Week 169, Week 197 and at EOS/Safety Follow-up, and includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory and gastrointestinal systems. Breast, genital, and rectal examinations are not required, unless warranted in opinion of the health care provider. The examination will be performed by a physician, or a nurse practitioner or physician's assistant under the supervision of a physician. If applicable, limited or symptom-directed examinations will be performed at all other specified time points, prior to study drug administration. A limited examination or symptom-directed examination should focus on the affected organ system or body area. Record new or worsened clinically significant abnormalities on the AE eCRF. Height (cm) does not need to be collected in Part 2 OLE.

b A complete neurological examination will be performed at Week 121, Week 145, Week 169, Week 197 and at EOS/Safety Follow-up, and includes the evaluation of consciousness, orientation, cranial nerves, motor and sensory system, coordination and gait, and reflexes. If applicable, limited or symptom directed examinations will be performed at all other specified time points, prior to study drug administration. A limited examination or symptom-directed examination should focus on the organ system or affected body area. Record new or worsened clinically significant abnormalities as AEs on the AE eCRF.

c Vital signs will be recorded after the participant has been resting for at least 5 minutes in the supine position. On dosing days, vital signs will be recorded prior to infusion (pre-dose) and within 15 minutes after the end of infusion, and once at all other specified time points as indicated. Weight (kg) will be collected at the same visits that vital signs are taken.

d Triplicate 12-lead ECGs will be obtained after the participant has been in the supine position for $\geqslant$5 minutes. On specified dosing days, ECG will be obtained prior to study drug administration and within 60 minutes after the end of the infusion, and once at all other specified time points as indicated. Additional ECG monitoring must be performed during treatment period if clinically indicated.

e Details on timing of vital signs, serum PK samples, triplicate ECGs, serum ADA samples, progranulin plasma samples, and exploratory plasma PD biomarker samples, are provided in protocol Table 9.

f Samples will be collected prior to study drug administration (if applicable).

g All women of childbearing potential will have urine pregnancy tests at specified visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

h Blood serum samples will be collected for determination of ADA prior to study drug administration (if applicable). Additional ADA samples should be collected in participants with signs and symptoms of infusion-related reactions. A sample of blood should be obtained for PK serum and ADA assessment of AL001, and testing should be performed for C-reactive protein, tryptase, and Interleukin 6 (IL-6).

i If the assessment is unable to be performed at the scheduled visit due to the COVID-19 pandemic, the assessments may be performed at a future on-site visit with approval from the medical monitor. Refer to protocol Appendix 3 for additional details on trial adaptations due to COVID-19.

j During study drug treatment, magnetic resonance imaging to be performed within ±7 days of a treatment visit.

k A diagnostic characterization form will be completed for symptomatic patients at Week 197/Part 2 EOS. It will also be completed for any asymptomatic participant who becomes symptomatic during the course of the study; for these participants, the diagnostic characterization form will be completed only at the first visit in which they exhibit clinical symptomatology.

l The COAs consist of the Clinical Dementia Rating Scale plus behavior and language domains from the National Alzheimer's Disease Coordinating Center Frontotemporal Lobar Degeneration module, Frontotemporal Dementia Rating Scale, Clinical Global Impression of Improvement, Clinical Global Impression of Severity, Color Trails Test Part 2, and the Repeatable Battery for the Assessment of Neuropsychological Status. Neurocognitive and functional tests will be performed prior to study drug administration (if applicable) and prior to any stressful procedures (e.g., blood collections, imaging).

m Winterlight Labs Speech Assessments (WLA) (for US, UK, and Canadian participants who agree to participate in the optional assessments only) will be conducted at home. Participants will have the option to complete the WLA after assessment visits only (WLA-A), after treatment visits only (WLA-B) or both (WLA-A and WLA-B). Assessments are conducted at home within ±7 days of the visit and will be supervised by the study partner. The study partner will be asked to complete a questionnaire online within ±7 days of the EOS visit.
n All AEs and SAEs must be recorded and reported, regardless of cause or relationship, that occur after the participant signs informed consent and through the Part1/Part2 EOS or Safety Follow-up visit, whichever is later. Any unresolved AEs and SAEs will be followed up through satisfactory clinical resolution. Additionally, SAEs considered related to study drug which occur at any time during the study will be reported by the investigator regardless of the AE/SAE collection window. At every study visit, participants will be asked a standard non-leading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (prescription drugs, herbal products, vitamins, minerals, vaccines, topical medications, and over-the-counter medications). Review of AEs and concomitant medications will be performed before and after study drug administration (when applicable).
o At Week 197, participants who complete the Part 2 96-week OLE period will complete a Part 2 EOS visit at the scheduled Week 197 timepoint. Participants who complete Visit 51/Week 197 will return for a Safety Follow-up visit 10 weeks after their last AL001 administration (Week 207, +/- 7 days).
p Participants who discontinue study drug and/or all assessments prior to completing the 96-week Part 2 treatment period will complete a Part 2 EOS visit as soon as possible after the decision is made.
q A Safety Follow-up visit will be performed 10 weeks following the last dose of AL001. The Safety Follow-up visit may be substituted by a scheduled visit if it occurs within the same window.

14.6. Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarker Sample and Imaging Assessments – Part 2 (Optional OLE)

Timepoint	Vital Signs	Serum PK sample [a]	Triplicate ECG	Serum ADA sample	Progranulin plasma sample	Exploratory plasma PD biomarker samples [b]
V27 (Week 101): Pre-dose	x					
V27 (Week 101): End of infusion	x					
V28 (Week 105): Pre-dose	x					
V28 (Week 105): End of infusion	x					
V29 (Week 109): Pre-dose	x					
V29 (Week 109): End of infusion	x					
V30 (Week 113): Pre-dose	x					
V30 (Week 113): End of infusion	x					
V31 (Week 117): Pre-dose	x					
V31 (Week 117): End of infusion	x					
V32 (Week 121): Pre-dose	x	x	x	x	x	x
V32 (Week 121): End of infusion	x	x	x	x	x	x
V33 (Week 125): Pre-dose	x					
V33 (Week 125): End of infusion	x					
V34 (Week 129): Pre-dose	x					
V34 (Week 129): End of infusion	x					
V35 (Week 133): Pre-dose	x					
V35 (Week 133): End of infusion	x					
V36 (Week 137): Pre-dose	x					
V36 (Week 137): End of infusion	x					
V37 (Week 141): Pre-dose	x					
V37 (Week 141): End of infusion	x					
V38 (Week 145): Pre-dose	x	x	x	x	x	x

Timepoint	Vital Signs	Serum PK sample [a]	Triplicate ECG	Serum ADA sample	Progranulin plasma sample	Exploratory plasma PD biomarker samples [b]
V38 (Week 145): End of infusion	x	x	x	x	x	x
V39 (Week 149): Pre-dose	x					
V39 (Week 149): End of infusion	x					
V40 (Week 153): Pre-dose	x					
V40 (Week 153): End of infusion	x					
V41 (Week 157): Pre-dose	x					
V41 (Week 157): End of infusion	x					
V42 (Week 161): Pre-dose	x					
V42 (Week 161): End of infusion	x					
V43 (Week 165): Pre-dose	x					
V43 (Week 165): End of infusion	x					
V44 (Week 169): Pre-dose	x	x	x	x	x	x
V44 (Week 169): End of infusion	x	x	x	x	x	x
V45 (Week 173): Pre-dose	x					
V45 (Week 173): End of infusion	x					
V46 (Week 177): Pre-dose	x					
V46 (Week 177): End of infusion	x					
V47 (Week 181): Pre-dose	x					
V47 (Week 181): End of infusion	x					
V48 (Week 185): Pre-dose	x					
V48 (Week 185): End of infusion	x					
V49 (Week 189): Pre-dose	x					
V49 (Week 189): End of infusion	x					
V50 (Week 193): Pre-dose	x					
V50 (Week 193): End of infusion	x					
V51 (Week 197): Pre-dose	x	x	x	x	x	x

V51 (Week 197): End of infusion	x	x	x	x	x	x
Safety Follow-up	x	x	x	x	x	
Part 2: EOS	x	x	x	x	x	x

Abbreviations: ADA, anti-drug antibody; ECG, electrocardiogram; EOS, End of Study; EOT, End of Treatment; hr, hour; PD, pharmacodynamic; PK, pharmacokinetic; V, visit;

[a] The window for serum PK samples is within 15 minutes after the end of the infusion.

[b] Exploratory PD biomarkers include Neurofilament Light chain, [redacted] in plasma and other analytes.