CLINICAL STUDY PROTOCOL

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AL001 in Individuals at Risk For or With Frontotemporal Dementia Due to Heterozygous Mutations in the Progranulin Gene

AL001-3

Investigational Product:	AL001, human recombinant anti-human sortilin IgG1 monoclonal antibody
Indication:	Frontotemporal Dementia (FTD)
Study Phase:	3
IND Number:	[redacted]
EUDRACT Number:	2019-004066-18
ClinicalTrials.gov Identifier:	NCT04374136
Sponsor:	Alector, Inc. 131 Oyster Point Boulevard, Suite 600 South San Francisco, CA 94080, US Telephone: +1 650-837-0384
Sponsor Medical Monitor:	Giacomo Salvadore, MD [redacted]
Version of Protocol:	Version 6.6
Date of Protocol:	30 July 2025
Previous Versions:	Version 6.0 (07 Sep 2023) Version 6.1 Germany (12 Sep 2023) Version 6.2 France (12 Sep 2023) Version 6.3 UK (12 Sep 2023) Version 6.4 Italy (13 Dec 2023) Version 6.5 European Union (01 Feb 2024) Version 5.0 (18 Nov 2021) Version 5.1 Germany (21 Dec 2021) Version 5.2 France (20 Dec 2021) Version 5.3 United Kingdom (20 Dec 2021) Version 4.0 (09 Feb 2021) Version 3.0 (04 Nov 2020) Version 2.0 (20 Dec 2019) Version 2.1 Belgium (07 Jul 2020) Version 2.2 Germany (25 May 2020) Version 2.3 Sweden (13 Jul 2020) Original Protocol Version 1.0 (25 Nov 2019)

CONFIDENTIAL

This document contains confidential information. This document must not be disclosed to anyone other than the site study staff and members of the institutional review board, independent ethics committee, institutional scientific review board, or equivalent. The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Alector, Inc.

PROTOCOL APPROVAL - SPONSOR SIGNATORY

Study Title	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AL001 in Individuals at Risk For or With Frontotemporal Dementia Due to Heterozygous Mutations in the Progranulin Gene
Protocol Number	AL001-3, Version 6.6
Protocol Date	30 Jul 2025

Protocol approved by:

Giacomo Salvadore, MD
[redacted]

Alector, Inc.
131 Oyster Point Boulevard, Suite 600
South San Francisco, CA 94080, USA

See signature manifest at the end of the document.

Signature Date

PROTOCOL APPROVAL - LEAD STATISTICIAN

Study Title	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AL001 in Individuals at Risk For or With Frontotemporal Dementia Due to Heterozygous Mutations in the Progranulin Gene
Protocol Number	AL001-3, Version 6.6
Protocol Date	30 Jul 2025

Protocol approved by:

Jinglin Zhong, Ph.D
[redacted]

Alector, Inc.
131 Oyster Point Boulevard, Suite 600
South San Francisco, CA 94080, USA

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Signature Date

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AL001 in Individuals at Risk For or With Frontotemporal Dementia Due to Heterozygous Mutations in the Progranulin Gene".

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Version 6.6, dated 30 Jul 2025, the International Council for Harmonisation (ICH) harmonised tripartite guideline E6(R2): Good Clinical Practice and all applicable government regulations. I agree to administer study treatment only to participants under my personal supervision or the supervision of a subinvestigator.

I will not supply the study treatment to any person not authorized to receive it. Confidentiality will be protected. Participant identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without written authorization from Alector, Inc.

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	Investigational Site Number

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Herein is a summary of the changes made to Version 6.0 of the protocol, dated 07 Sep 2023, and reflected in the amended Version 6.6 of the protocol, dated 30 Jul 2025.

Amended Protocol Sections	**Summary of Change(s)**	**Rationale**
Throughout	Typographical, formatting corrections, administrative changes, and text clarifications; updates to the Table of Contents, List of Tables, List of Figures, and List of Abbreviations.	Minor changes made to correct errors, conform to revised style standards, and/or reflect updates to the content.
Protocol Approval	Sponsor and lead statistician approver names updated.	Revised due to changes in project team at Sponsor.
Synopsis	Revised with all relevant updates included in the body of the protocol amendment detailed below.	Revised for consistency with updates to the body of the document.
Section 2 (Table 1)	Primary efficacy objective updated to clinical co-primary efficacy objective. Plasma PGRN exploratory objective updated to biomarker co-primary objective. Target population, variable of interest, intercurrent events and corresponding strategy, and population-level summary variable added for the biomarker co-primary objective. Exploratory objective FRS updated to secondary objective.	Per the FDA's review comments to the SAP, the Sponsor has agreed with the recommendation to change plasma PGRN concentration from an exploratory objective to a biomarker co-primary objective together with the clinical co-primary objective. Change FRS from an exploratory objective to a secondary objective to align with the hypothesis testing strategy to control type I error.
Section 8	Sample size calculation text and statistical analysis details revised to reflect the change in co-primary objectives. Details of supportive analyses added for the biomarker co-primary endpoint with reference to the SAP for full details of supportive and sensitivity analyses. Changes of full analysis sets naming.	Relevant changes to accommodate the change of co-primary objectives are made to the statistical hypotheses, sample size calculation, multiplicity adjustment and analysis set definitions. Additional analyses were also included as a result of the change to include biomarker co-primary objective.
Section 8.2	Sample size calculation text revised to reflect the change in co-primary objectives.	Revised to include texts to characterize the statistical power for the added biomarker co-primary endpoint under the current planned sample size.

Amended Protocol Sections	Summary of Change(s)	Rationale
Section 8.3.2	Updated to include the analyses that the analysis set will be used for.	Revised for clarity of the analysis population name to identify relevant subsets of participants.
Section 8.3.2.1	Changed wording from FAS1 to FAS-symptomatic. Updated to include the analyses that the analysis set will be used for.	Revised for clarity of the analysis population name to identify relevant subsets of participants.
Section 8.3.2.2	Changed wording FAS2 to FAS-at risk. Updated to include the analyses that the analysis set will be used for.	Revised for clarity of the analysis population name to identify relevant subsets of participants.
Section 8.4	Added subgroup analyses for the co-primary biomarker endpoint.	Aligned with the level of details provided for the clinical co-primary endpoint.
Section 8.5.2.1	Updated text to reflect the new status of clinical co-primary objective.	Revised for consistency with new co-primary objectives.
Section 8.5.2.2	Added section for the biomarker co-primary objective including statistical model, statistical hypotheses, and analysis set.	Added section for the biomarker co-primary objective.
Section 8.5.2.5	Removed mention of different testing strategies for the FDA and the EMA.	Updated multiplicity adjustment based on new hypothesis testing strategy.
Section 8.5.4.2	Minor text edits to align with the planned analyses.	Revised for clarity with the planned analyses.
Section 12.2.2	Updated definition of major protocol deviations.	Revised for consistency with the draft guidance on protocol deviations from the FDA, dated 30 December 2024.
Section 13	Additional reference added as required due to changes to other sections.	Additional reference added due to change in plasma PGRN biomarker from exploratory to co-primary endpoint.

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PROTOCOL SYNOPSIS

<table>
<tr><td colspan="3">Protocol Number: AL001-3</td></tr>
<tr><td colspan="3">Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AL001 in Individuals at Risk For or With Frontotemporal Dementia Due to Heterozygous Mutations in the Progranulin Gene</td></tr>
<tr><td colspan="3">Sponsor: Alector, Inc.
131 Oyster Point Boulevard, Suite 600
South San Francisco, CA 94080, USA</td></tr>
<tr><td colspan="3">Study Phase: 3</td></tr>
<tr><td colspan="3">Investigational Sites: Approximately 60 investigational sites globally</td></tr>
<tr><td colspan="3">Indication: Frontotemporal dementia (FTD)</td></tr>
<tr><td colspan="3">Part 1 Double-Blind, Placebo-Controlled Treatment Period: Study Objectives and Endpoints</td></tr>
<tr><td></td><td>Objectives</td><td>Estimand/Endpoint</td></tr>
<tr><td rowspan="4">Co-primary Efficacy</td><td rowspan="4">To evaluate the efficacy of AL001 compared with placebo in symptomatic participants as measured by the CDR® plus NACC FTLD-SB</td><td>Target population: Symptomatic carriers of a GRN mutation causative of FTD as defined by the inclusion and exclusion criteria.</td></tr>
<tr><td>Variable of interest: Change from baseline to Weeks 48, 72, and 96 in the CDR® plus NACC FTLD-SB.</td></tr>
<tr><td>Intercurrent events and corresponding strategy: Study treatment discontinuation/prohibited concomitant medications (Treatment Policy). All observed values of the variable of interest, regardless of whether or not the participant has discontinued treatment/taken a prohibited medication.</td></tr>
<tr><td>Population-level summary variable: Percent reduction of the placebo group change from baseline across Weeks 48, 72, and 96.</td></tr>
<tr><td rowspan="3">Co-primary Biomarker</td><td rowspan="3">To evaluate the treatment effect of AL001 compared with placebo in symptomatic participants as measured by plasma PGRN concentration</td><td>Target population: Symptomatic carriers of a GRN mutation causative of FTD as defined by the inclusion and exclusion criteria.</td></tr>
<tr><td>Variable of interest: Change from baseline of the log-10 transformed values at Week 96 in plasma PGRN concentration.</td></tr>
<tr><td>Intercurrent events and corresponding strategy: Study treatment discontinuation/prohibited concomitant medications (Treatment Policy). All observed values of the variable of interest, regardless of whether or not the participant has discontinued treatment/taken a prohibited medication.</td></tr>
</table>

		Population-level summary variable: Mean change from baseline of log-10 transformed concentrations in the treatment group relative to the placebo group at Week 96.
Secondary Efficacy	To evaluate the efficacy of AL001 compared with placebo in symptomatic participants as measured by CGI-S	**Target population:** Symptomatic carriers of a *GRN* mutation causative of FTD as defined by the inclusion and exclusion criteria.
		Variable of interest: Change from baseline to Weeks 48, 72, and 96 on the CGI-S.
		Intercurrent events and corresponding strategy: Study treatment discontinuation/prohibited concomitant medications (Treatment Policy). All observed values of the variable of interest, regardless of whether or not the participant has discontinued treatment/taken a prohibited medication.
		Population-level summary variable: Percent reduction of the placebo group change from baseline across Weeks 48, 72, and 96.
Secondary Efficacy	To evaluate the efficacy of AL001 compared with placebo in symptomatic participants as measured by the FRS	**Target population:** Symptomatic carriers of a *GRN* mutation causative of FTD as defined by the inclusion and exclusion criteria.
		Variable of interest: Change from baseline to Week 48, 72 and 96 in the FRS.
		Intercurrent events and corresponding strategy: Study treatment discontinuation/prohibited concomitant medications (Treatment Policy). All observed values of the variable of interest, regardless of whether or not the participant has discontinued treatment/taken a prohibited medication.
		Population-level summary variable: Percent reduction of the placebo group values across Weeks 48, 72, and 96.
Secondary Efficacy	To evaluate the efficacy of AL001 compared with placebo in symptomatic participants as measured by CGI-I	**Target population:** Symptomatic carriers of a *GRN* mutation causative of FTD as defined by the inclusion and exclusion criteria.
		Variable of interest: Actual values at Weeks 48, 72, and 96 on the CGI-I.
		Intercurrent events and corresponding strategy: Study treatment discontinuation/prohibited concomitant medications (Treatment Policy). All observed values of the variable of interest, regardless of whether or not the participant

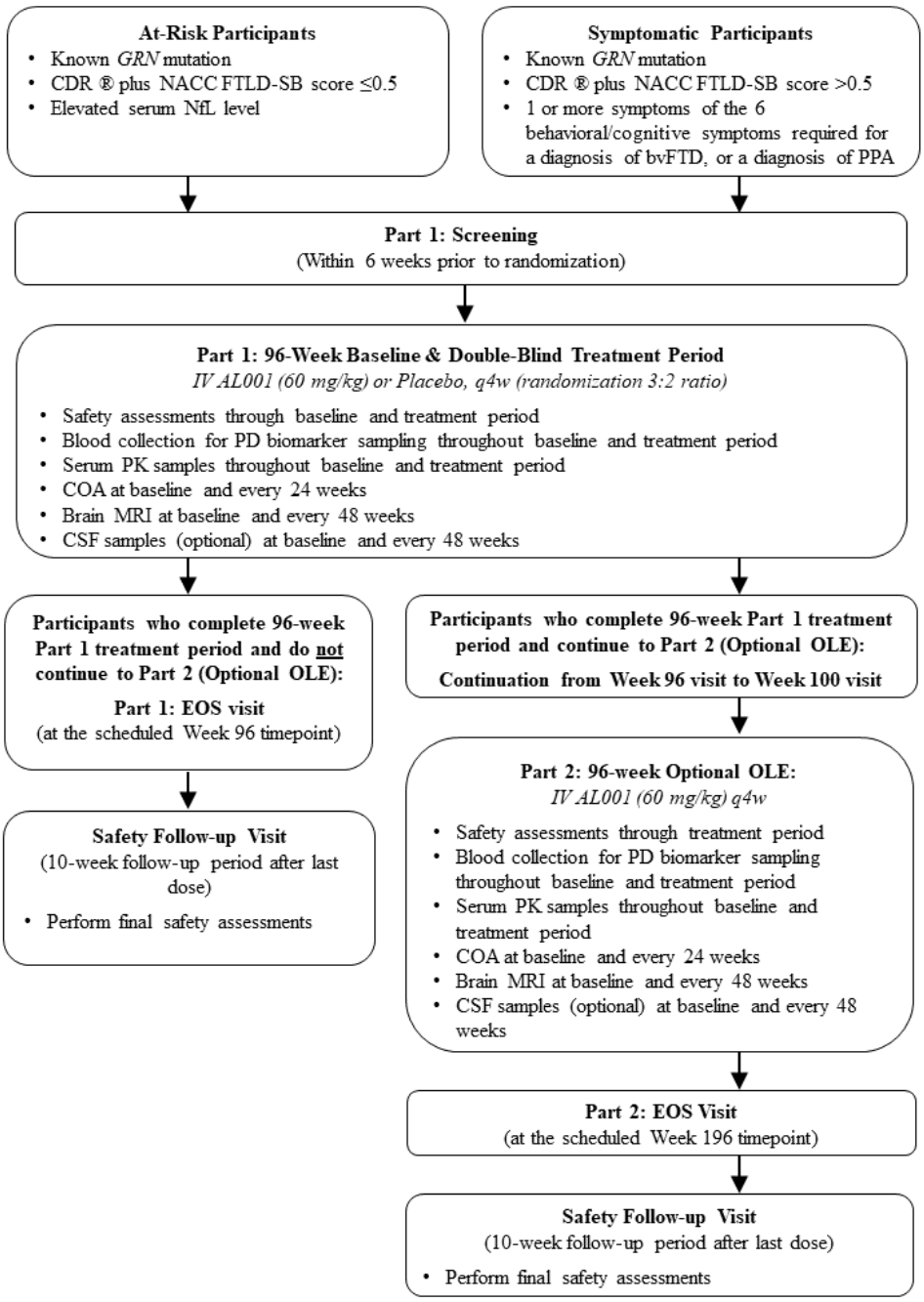
		has discontinued treatment/taken a prohibited medication.
		Population-level summary variable: Percent reduction of the placebo group values across Weeks 48, 72, and 96.
Secondary Efficacy	To evaluate the efficacy of AL001 compared with placebo in symptomatic participants as measured by RBANS	**Target population:** Symptomatic carriers of a *GRN* mutation causative of FTD as defined by the inclusion and exclusion criteria.
		Variable of interest: Change from baseline to Weeks 48, 72, and 96 on the RBANS.
		Intercurrent events and corresponding strategy: Study treatment discontinuation/prohibited concomitant medications (Treatment Policy). All observed values of the variable of interest, regardless of whether or not the participant has discontinued treatment/taken a prohibited medication.
		Population-level summary variable: Percent reduction of the placebo group change from baseline across Weeks 48, 72, and 96.
Pharmacodynamic and Disease Biomarkers	To evaluate the treatment effect of AL001 compared with placebo as measured by pharmacodynamic and disease pathology biomarkers in the symptomatic population, the at-risk population, and all FTD participants (both symptomatic and at-risk).	• PGRN concentrations in optional CSF • Neurofilament light chain (NfL) concentrations in serum and optional CSF • Structural volumetric MRI whole and regional brain volume
Safety	To evaluate the safety and tolerability of AL001 compared with placebo as measured by safety assessments and antidrug antibodies (ADAs) in the symptomatic population, the at-risk population, and all FTD participants (both symptomatic and at-risk).	• Incidence, nature, and severity of adverse events (AEs) and serious adverse events (SAEs) • Physical examination abnormalities • Neurological examination abnormalities • Changes in vital signs from baseline over time • Changes in electrocardiograms from baseline over time • MRI abnormalities • Changes in clinical laboratory tests from baseline over time • Sheehan-STS • Incidence of ADAs to AL001
Exploratory Endpoints	To evaluate the effects of AL001 compared with placebo as measured by:	
	Exploratory Quality of Life Objective:	*Exploratory Quality of Life Endpoints:*

	• Quality of Life COAs	• EQ5D score • ZBI score
	Exploratory Pharmacoeconomic Objective: • Pharmacoeconomic COA	*Exploratory Pharmacoeconomic Endpoint:* • RUD-Lite score
	Exploratory PD and Disease Biomarker Objective: • Exposure-response relationships • Exploratory imaging	*Exploratory PD and Disease Biomarker Endpoints:* • Exposure-response relationships for relevant biomarkers (eg, PGRN, NfL), efficacy, or safety responses in relation to AL001 exposure • Arterial spin labeling, diffusion-tensor imaging, and other MRI measures
	Exploratory COA Objective: • WLA	*Exploratory COA Endpoints:* • WLA, for participants who agree to participate in these optional assessments only
Part 2 Optional Open-Label Extension: Study Objectives and Endpoints		
	Objectives	**Endpoint**
Primary	To assess the long-term safety and tolerability of AL001 in participants who have completed Part 1 of the study	• Incidence, nature, and severity of AEs and SAEs • Physical examination abnormalities • Neurological examination abnormalities • Changes in vital signs from baseline over time • Changes in electrocardiograms from baseline over time • MRI abnormalities • Changes in clinical laboratory tests from baseline over time • Sheehan-STS • Incidence of ADAs to AL001
Exploratory Endpoints	COAs, correlative assessments (eg, 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 Part 1 of the study on the following:	

	• Treatment effect of AL001 compared with placebo as measured by disease pathology biomarkers	• PGRN concentrations in plasma • NfL concentrations in serum • Structural volumetric MRI whole and regional brain volume; arterial spin labeling, diffusion-tensor imaging, and other MRI measures
	• Clinical progression as measured by COAs	The overall change from baseline on the scores of the instruments in the COAs • CDR® plus NACC FTLD • CGI-I • CGI-S • RBANS • FRS • WLA, for participants who agree to participate in these optional assessments only
	• Quality of Life COAs	• EQ-5D score • ZBI score
	• Pharmacoeconomic COA	• RUD-Lite score
	• Exposure-response relationships	• Exposure-response relationships for relevant biomarkers (eg, PGRN, NfL), efficacy, or safety responses in relation to AL001 exposure
ADA=antidrug antibody; CDR® plus NACC FTLD-SB=Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center frontotemporal lobar degeneration Behavior and Language Domains Sum of Boxes; CGI-I=Clinical Global Impression-Improvement; CGI-S=Clinical Global Impression-Severity; COA=clinical outcome assessment; CSF=cerebrospinal fluid; EQ5D=European Quality of Life-5 Dimensions; FRS=Frontotemporal Dementia Rating Scale; FTD=frontotemporal dementia; *GRN*=progranulin gene; MRI=magnetic resonance imaging; NfL=neurofilament light chain; OLE=open-label extension; PD=pharmacodynamic; PGRN=progranulin protein; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; RUD-Lite=Resource Utilization in Dementia-Lite version; SAE=serious adverse event; Sheehan-STS=Sheehan-Suicidality Tracking Scale; WLA=Winterlight Labs Speech Assessments; ZBI=Zarit Burden Interview.		
Number of Participants Planned:	Approximately 110 participants will be enrolled at approximately 60 investigational sites globally, with a minimum of 90 symptomatic participants.	
Study Population:	Male and female participants 25 to 85 years of age at risk for or with FTD due to heterozygous loss-of-function mutations in the *GRN* gene.	
Study Design:	The study has 2 parts: A double-blind, placebo-controlled treatment period (Part 1), followed by an open-label extension (OLE) period (Part 2). Part 1 is a 96-week, randomized, double-blind treatment period to evaluate the efficacy and safety of AL001 60 mg/kg compared to placebo administered every 4 weeks (q4w) in participants who are carriers of heterozygous loss-of-function GRN mutations causative of FTD.	

	Part 2 is an optional, 96-week OLE period for eligible participants who have completed Part 1. Part 2 will evaluate the long-term safety and tolerability of open-label AL001 60 mg/kg, q4w. Each participant must be a known carrier of a heterozygous loss-of-function GRN mutation causative of FTD with a global Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center frontotemporal lobar degeneration Behavior and Language Domains (CDR® plus NACC FTLD) score of 0 to 2, and: • Participants with a CDR® plus NACC FTLD Sum of Boxes (CDR® plus NACC FTLD-SB) score ≤0.5 must have an elevated serum NfL (at-risk participants), or • Participants with a CDR® plus NACC FTLD-SB score >0.5 must have 1 or more of the 6 behavioral/cognitive symptoms required for a diagnosis of possible behavioral variant frontotemporal dementia (bvFTD; Rascovsky 2011), or a diagnosis of primary progressive aphasia (PPA; Gorno-Tempini 2011) (symptomatic participants). **Part 1 (Double-Blind, Placebo-Controlled Treatment Period):** Part 1 of the study is a 96-week, randomized, double-blind, placebo-controlled treatment period to evaluate the efficacy and safety of AL001 compared to placebo in participants who are carriers of heterozygous loss-of-function *GRN* mutations causative of FTD. Eligible participants will be randomly assigned, in a double-blind fashion, to receive AL001 (60 mg/kg) or placebo in a 3:2 ratio (AL001:placebo), and stratified by: • CDR® plus NACC FTLD-SB score ≤0.5 • CDR® plus NACC FTLD global score 0.5 (with a CDR® plus NACC FTLD-SB >0.5) • CDR® plus NACC FTLD global score 1 • CDR® plus NACC FTLD global score 2 **Part 2 (Optional Open-Label Extension Period):** Part 2 of the study is an optional 96-week, OLE to assess the long-term safety and tolerability of AL001 in participants who have completed Part 1 of the study. Continuation in the OLE is optional for Part 1 participants. A Part 1 participant may be excluded from continuing in the Part 2 OLE if, in the opinion of the Investigator, continued treatment with AL001 at the conclusion of Part 1 is not beneficial or safe for the participant. Part 1 participants who have been admitted to a nursing home/assisted living facility are not eligible for participation in the OLE. Treatment assignment in Part 1 (AL001 or placebo) will remain blinded to investigators and participants until Part 2 has been completed and the Part 2 data for all participants have been cleaned and locked. In addition, the Sponsor will remain blinded to treatment assignment in Part 1 until Part 1 has been completed and the Part 1 data for all participants have been cleaned and locked. All participants in the OLE, whether they received AL001 or placebo in Part 1, will receive open-label AL001 at a dose of 60 mg/kg, q4w. An individual participant may continue to receive AL001 (60 mg/kg) in the OLE portion of the study for up to 25 doses over a 96-week dosing period for a total exposure of up to 196 weeks.

Study Design



bvFTD=behavioral variant frontotemporal dementia; CDR® plus NACC FTLD=Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center frontotemporal lobar degeneration Behavior and Language Domains; COA=clinical outcome assessment; CSF=cerebrospinal fluid; EOS=end of study; *GRN*=progranulin gene; IV=intravenous(ly); MRI=magnetic resonance imaging; NfL=neurofilament light chain; OLE=open-label extension; PD=pharmacodynamic; PK=pharmacokinetic; PPA=primary progressive aphasia; q4w=every 4 weeks.

Duration of Participation:	**Part 1 (Double-Blind, Placebo-Controlled Treatment Period)** • A screening period (within 6 weeks prior to Randomization) • A treatment period (96 weeks, Day 0 through Week 96) • Participants who discontinue study treatment prior to completing the 96-week Part 1 treatment period should be encouraged to complete all remaining scheduled assessment visits through Part 1 (including Clinical outcome assessments [COAs], magnetic resonance imaging [MRI], and CSF evaluations). – A Part 1 End of Treatment (EOT) visit will be completed by participants who discontinue study treatment 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 Safety Follow-up visit will be performed 10 weeks after their last study treatment administration. – A Part 1 End of Study (EOS) visit will be completed by participants who discontinue study treatment and all assessments. Part 1 EOS assessments should be completed as soon as possible after the decision is made. A Safety Follow-up visit will be performed 10 weeks after their last study treatment administration. Participants who complete the Part 1 96-week treatment period will have the option to receive open-label AL001 in Part 2 (OLE) of the study. – Participants who do not continue in Part 2 will complete a Part 1 EOS visit at the scheduled Week 96 visit. A Safety Follow-up visit will be performed 10 weeks after the participant's last study treatment administration. – Participants who continue in Part 2 will complete the Week 96 visit and enter Part 2 at the Week 100 visit. **Part 2 (Optional Open-Label Extension Period)** • A treatment period (96 weeks, Week 100 through Week 196), or until AL001 is commercially available in the country where the participant is being treated, whichever is earlier. • Participants who discontinue AL001 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. A Safety Follow-up visit will be performed 10 weeks after their last study treatment administration. At Week 196, participants who complete the Part 2 96-week OLE period will complete a Part 2 EOS visit at the scheduled Week 196 time point. A Safety Follow-up visit will be performed 10 weeks after the participant’s last study treatment administration unless they will continue to receive AL001 under another Alector protocol or program.

Description of Study Procedures:	**Part 1 (Double-Blind, Placebo-Controlled Treatment Period)** *Optional Pre-Screening to Confirm Presence of Known Genetic Mutations Associated with Frontotemporal Dementia (including GRN Mutations)* All study participants must be known carriers of a heterozygous loss-of-function *GRN* mutation causative of FTD to be eligible to participate in the study (see Part 1 Eligibility Criterion #1). Participants may be pre-screened to determine the presence of a *GRN* mutation. If pre-screening is required, the participant must provide informed consent for the pre-screening assessment of the presence of a *GRN* mutation and other known common genetic mutations associated with Frontotemporal Dementia, with genetic counseling highly recommended. *Optional Pre-Screening to Confirm Presence of Elevated Serum NfL Levels* At-risk study participants (CDR® plus NACC FTLD-SB score ≤0.5) must have an elevated serum NfL level. Participants may be pre-screened to determine if their serum NfL level is elevated. If pre-screening is required, the participant must provide informed consent for the pre-screening assessment of the serum NfL levels. Elevated serum NfL levels obtained ≤90 days prior to study treatment administration can be used to satisfy eligibility. *Screening Period* To determine eligibility for entry into Part 1 of the study, participants must provide informed consent. Screening procedures may be performed within 6 weeks prior to randomization (Day -42 to Day 0). Participants will undergo a screening evaluation with MRI, blood sampling for NfL biomarker measurement, routine safety laboratory, and other safety assessments. COAs, including those performed by the participant and their study partner, will be conducted at Screening. For participants who consent to optional lumbar punctures, CSF will also be collected at baseline prior to study treatment administration. *Randomization* Eligible participants will be randomly assigned to receive AL001 or placebo. Randomization will occur prior to or on Day 0. Study treatment administration on Day 0 will not be administered until all baseline assessments are completed and the participant has met all eligibility criteria. *Double-Blind Treatment Period* The planned study treatment period will be 96 weeks. Study treatment (AL001 60 mg/kg or placebo) will be administered IV q4w for a total of 25 doses. Clinical outcome assessments, including those performed by the participant and their study partner, will be conducted every 24 weeks. Imaging will be performed every 48 weeks. Optional lumbar puncture for CSF collection will be performed every 48 weeks. Every effort will be made to follow all randomized participants for the full 96-week study treatment period, regardless of whether they discontinue study treatment. All participants will be followed for safety at 10 weeks after the last dose of AL001. Upon completion of the double-blind study treatment period (Week 96), participants who are eligible and provide consent will continue in Part 2 (Optional OLE) of the study. Part 1 participants who do not continue in Part 2 (Optional OLE) of the study will return to the investigational site 10 weeks after their last dose of study treatment for final safety assessments. **Part 2 (Optional Open-Label Extension Period)** *Eligibility Confirmation* There is no screening period for participants who elect to enroll in Part 2 (OLE) of the study. Participants who, after completing Part 1, provide informed consent to participate in Part 2 and meet all the eligibility criteria for the OLE (determined prior to study

	treatment administration at Week 100), may receive open-label AL001 according to the OLE administration schedule. *Treatment Period* The Part 2 OLE period will be up to 96 weeks. Open-label AL001 60 mg/kg will be administered IV q4w for a total of up to 25 doses. Blood sampling for safety, clinical outcome assessments, including those performed by the participant and their study partner, and imaging will be performed. OLE participants who discontinue study treatment early (eg, due to participant decision, withdrawal criteria, or AL001 commercial availability in the country where the participant in being treated) will be followed for safety at 10 weeks after the last dose of AL001.
Inclusion/Exclusion Criteria - Part 1 (Double-Blind, Placebo-Controlled Treatment Period)	**Inclusion Criteria** Each prospective participant must meet all of the following criteria to be enrolled in this study: 1. Is a known carrier of a heterozygous loss-of-function *GRN* mutation causative of FTD with a global CDR® plus NACC FTLD score of 0 to 2, and: • A CDR® plus NACC FTLD-SB score ≤0.5 with an elevated level of serum NfL, or • A CDR® plus NACC FTLD-SB score of >0.5 with 1 or more of the 6 behavioral/cognitive symptoms required for a diagnosis of possible bvFTD (Rascovsky 2011), or a diagnosis of PPA (Gorno-Tempini 2011). 2. Age 25 to 85 years, inclusive, at Screening. 3. At Screening, women must be nonpregnant and nonlactating, and 1 of the following conditions must apply: a. Not a woman of childbearing potential (WOCBP) (either surgically sterilized or physiologically incapable of becoming pregnant, or at least 1-year post-menopausal [amenorrhea duration of 12 consecutive months with no identified cause other than menopause]). b. Is a WOCBP and agrees to use an acceptable contraceptive method from Screening until 10 weeks after the last dose of study treatment. Acceptable contraception is defined as using hormonal contraceptives (eg, combined oral contraceptive pill) or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm, cervical cap, or condom. In addition, total abstinence, if in accordance with the lifestyle of the participant, is acceptable. c. WOCBP must have a serum pregnancy test conducted at screening. Additional requirements for pregnancy testing during and after study intervention are described in the Schedules of Assessments. 4. Men must agree to use acceptable contraception and not donate sperm from Day 0 until 10 weeks after the last dose of study treatment. Acceptable contraception for the male participant when having sexual intercourse with a WOCBP who is not currently pregnant is defined as using a condom. In addition, WOCBP partners must use hormonal contraceptives (eg, combined oral contraceptive pill) or an intrauterine device. 5. Agrees not to donate blood or blood products for transfusion for the duration of the study and for 1 year after the final dose of study treatment. 6. Willing to and can comply with the study protocol requirements, in the opinion of the Investigator.

7. Willing and able to give informed consent. If the patient is not competent, a legally authorized representative must provide informed consent on their behalf, and the patient must provide assent, in accordance with local regulations, guidelines, and institutional review board (IRB) or independent ethics committee (IEC).
8. Patient has the availability of a person ("study partner") who has frequent and sufficient contact with the patient (at least 5 hours per week of in-person contact) and who can provide accurate information to the study site regarding the patient's behavior, cognitive, and functional abilities, as well as their health, throughout the study. Requirements for the study partner include:
    a. Willing and able to provide informed consent to participate in the study as a study partner.
    b. The study partner must have sufficient cognitive capacity to accurately report upon the participant's behavior, cognitive, and functional abilities, in the opinion of the Investigator.
    c. The study partner should be in sufficiently good general health to have a high likelihood of maintaining the same level of interaction with the participant and participation in study procedures throughout the study duration.
    d. The same study partner should participate throughout the duration of Part 1 of the study. If a change in study partner is necessary, the Medical Monitor must be contacted.
    e. Study partner agrees to provide information at investigational site visits that require partner input for COA completion.
    f. Study partner agrees to accompany the participant at COA visits, as follows:
        - **At-risk participants** (CDR® plus NACC FTLD-SB score ≤0.5) require the study partner at the COA visits only.
        - **Symptomatic participants** (CDR® plus NACC FTLD-SB score >0.5) require the study partner at each visit.
        - **At-risk participants who become symptomatic** (CDR® plus NACC FTLD-SB >0.5) during the study treatment period require the study partner at each visit moving forward through Study Completion.

Inclusion criteria applicable to those participants participating in the optional Winterlight Labs Speech Assessment (WLA) only:

1. Has available and willing study partner to administer the WLA.
2. Has WiFi access in their residence or WiFi access in a private area where the testing can take place.
3. Participants and study partners must be proficient in English, Spanish, French, Dutch, or German in the Investigator's opinion.

Exclusion Criteria

Prospective participants meeting any of the following criteria will be excluded from the study:

1. Dementia due to a condition other than FTD including, but not limited to, Alzheimer's disease, Parkinson's disease, dementia with Parkinsonism, rapid eye movement (REM) behavior disorder, dementia with Lewy bodies, Huntington disease, or vascular dementia.
2. Known mutation causative of neurodegenerative disorder(s) other than heterozygous loss-of-function *GRN* mutations causative of FTD.

	3. Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins. 4. Signs or symptoms of progressive supranuclear palsy or bulbar dysfunction, such as postural instability, eye problems, and swallowing difficulties. 5. History of moderate or severe substance use disorder within the past 2 years, with the exception of nicotine, as defined by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition criteria (American Psychiatric Association 2013). 6. Clinically significant vitamin B12 or folate deficiency (if treated, must be on a stable regimen for at least 3 months prior to first study treatment administration). 7. Untreated hypothyroidism (if treated, thyroid supplementation dose must be stable for at least 3 months with a normal thyroid-stimulating hormone level prior to study treatment administration). 8. Insufficiently controlled diabetes mellitus (eg, hemoglobin A1C ≥8%). 9. Any surgery (major or emergent) or hospitalization within 30 days prior to first study treatment administration. 10. Participant has a history of cancer except if it: a. Is considered likely to be cured or in remission for at least 12 months, b. Is not being actively treated with anticancer therapy or radiation and, in the opinion of the Investigator, is not likely to require treatment in the ensuing 3 years, c. Is considered to have low probability of recurrence (with supporting documentation from the treating oncologist if possible), including participants with ongoing antihormonal treatment (eg, tamoxifen), d. For prostate cancer, has not had significant progression within the past 2 years, and is stable and adequately controlled, e. For localized skin basal cell carcinoma or squamous cell carcinoma, the participant should continue with screening and seek treatment for the skin carcinoma. 11. Positive for hepatitis B surface antigen, human immunodeficiency virus 1 or 2 antibodies or antigen, or history of spirochetal infection of the central nervous system (CNS) (eg, syphilis, borreliosis, or Lyme disease). Participants with a positive or equivocal hepatitis C virus antibody will be allowed to enroll if hepatitis C RNA is confirmed negative. 12. Significant kidney disease as indicated by either of the following: a. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, according to the re-expressed abbreviated (4-variable) Modification of Diet in Renal Disease (MDRD) Study equation, Note: MDRD equation is as follows: eGFR (mL/min/1.73 m^2) = 175 × (standardized serum creatinine) - 1.154 × (Age) - 0.203 × (0.742 if female) × (1.212 if Black), or b. Creatinine ≥2 mg/dL 13. Impaired hepatic function as indicated by screening aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5 × the upper limit of normal

	(ULN), and total bilirubin ≥1.5 × ULN. Note: Participants with Gilbert's syndrome are eligible to participate if approved by the Medical Monitor. 14. Clinically significant hematologic abnormalities as indicated by hemoglobin ≤10 g/dL; white blood cells (WBC) ≤3,000/mm^3; absolute neutrophil count ≤1,000/mm^3; or platelet count ≤150,000/mm^3. 15. Participants with hypertension who are not adequately and stably controlled as per the American College of Cardiology/American Heart Association (ACC/AHA) guidelines. 16. History or presence of an abnormal electrocardiogram (ECG) that is clinically significant, including complete left bundle branch block, second- or third-degree atrioventricular block, or evidence of acute or subacute myocardial infarction or ischemia. 17. History of or concurrent clinically significant cardiovascular disease such as but not limited to myocardial infarction, angina pectoris, New York Heart Association Class III or IV cardiac failure, ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (eg, severe left ventricular systolic dysfunction, left ventricular hypertrophy). If the condition is stable per the consulting cardiologist, then the patient can enroll at the Investigator's discretion. 18. Clinically significant electrolyte abnormalities (eg, hypokalemia, hypomagnesemia, hypocalcemia). 19. For participants who consent to lumbar puncture, participant has contraindication to lumbar dural puncture, including coagulopathy, concomitant anticoagulation medication (except for a platelet inhibitor such as aspirin), thrombocytopenia, or other factor(s) that precludes safe lumbar puncture. 20. History or presence of clinically evident vascular disease potentially affecting the brain (eg, clinically significant carotid or vertebral artery stenosis or plaque; cerebral hemorrhage or infarct greater than 1 cm^3; 3 or more lacunar infarcts in any location; cerebral contusion; encephalomalacia; intracranial aneurysm; arteriovenous malformation; subdural hematoma); hydrocephalus; space occupying lesions (eg, abscess or brain tumor such as meningioma) that have the potential to affect cognitive function; or intracranial tumor that is clinically relevant (eg, glioma, cerebral metastasis). 21. History of a clinically significant, persistent neurologic deficit, structural brain damage, or CNS trauma. 22. Resides in a skilled nursing facility, convalescent home, or long-term care facility at screening; or requires continuous nursing care (ie, >3 months). 23. Unable to tolerate the required safety portion (as defined in the imaging manual) of MRI procedures (eg, due to anxiety or claustrophobia) or has a contraindication to MRI, including, but not limited to, the presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that are not compatible with an MRI scan; or any other clinical history or examination finding that would pose a potential hazard in combination with MRI. Use of conscious sedation is allowed to aid with tolerance of imaging procedures. 24. Has a medical condition or extenuating circumstance that, in the opinion of the Investigator, might compromise the participant's ability to comply with the protocol-required testing or procedures, or compromise the participant's well-being, safety, or clinical interpretability.

Inclusion/Exclusion Criteria - Part 2 (Optional OLE)	**Inclusion Criteria** The OLE is optional for participants who complete Part 1 of the study. Participants who complete Part 1 (96 weeks) of the study are eligible for continued treatment with AL001, provided that all of the following criteria are met: 1. Participant is willing and able to give informed consent to continue treatment with AL001. If the study participant is not competent, a legally authorized representative must provide informed consent on his or her behalf, and the participant must provide assent, in accordance with the local regulations, guidelines, and IRB or IEC. 2. Is willing and has the ability to comply with OLE requirements, in the opinion of the Investigator. 3. Has availability of a person ("study partner") who can continue to assist with assessments throughout the OLE evaluation period. The study partner must have frequent and sufficient contact with the participant (at least 5 hours per week of in-person contact), have the ability to provide accurate information regarding the participant's cognitive and functional abilities as well as their health throughout the study. Requirements for the study partner include: a. Willing and able to provide informed consent to participate in the study as a study partner. b. The study partner must have sufficient cognitive capacity to accurately report upon the participant's behavior, cognitive, and functional abilities, in the opinion of the Investigator. c. The study partner should be in sufficiently good general health to have a high likelihood of maintaining the same level of interaction with the participant and participation in study procedures throughout the study duration. d. The Part 2 study partner can be the same individual as in Part 1, or it can be a different individual, but the same Part 2 study partner should participate throughout the duration of Part 2. If a change in study partner during Part 2 is necessary, the Medical Monitor must be contacted. e. Study partner agrees to provide information at investigational site visits that require partner input for COA completion. f. Study partner agrees to accompany the participant at COA visits, as follows: – **At-risk participants** (CDR® plus NACC FTLD-SB score ≤0.5) require the study partner at the COA visits only. – **Symptomatic participants** (CDR® plus NACC FTLD-SB score >0.5) require the study partner at each visit. – **At-risk participants who become symptomatic** (CDR® plus NACC FTLD-SB >0.5) during the study treatment period require the study partner at each visit moving forward through Study Completion. **Exclusion Criteria** Part 1 participants are not eligible for continued treatment with AL001 in the OLE if any of the following apply: 1. Part 1 participant has been admitted to a skilled nursing facility, convalescent home, or long-term care facility at screening and requires continuous nursing care (ie, >3 months). 2. Part 1 participant has a medical condition or extenuating circumstance such that, in the opinion of the Investigator, continued treatment with AL001 at the conclusion of Part 1 is not beneficial or safe for the participant.

Prohibited and Restricted Medication Criteria - Part 1 and Part 2	**Medication-related Exclusion Criteria** The following medications are prohibited for a prespecified duration prior to Part 1 study start, as indicated, and during the entire period of study participation (Part 1 and Part 2). Participants who start these medications during the study at any time may be withdrawn from study treatment. 1. Any psychoactive cannabinoids at least 90 days prior to first study treatment administration on Part 1, unless approved by the Medical Monitor. Note: Cannabinoid use during the study is not permitted within 8 hours prior to any COA. Topical cannabinoid oil without tetrahydrocannabinol is allowable at any time. 2. Intermittent use of benzodiazepines or other sedatives (including second-generation antipsychotics used for sedation or anti-anxiolysis) during the 30 days prior to administration of first study drug. Chronic, stable use of these medications established for at least 90 days before administration of first dose is acceptable. If chronic stable use begins after Day 1 of Part 1, it is at the Investigator's discretion whether withholding is likely to adversely impact cognitive procedures. Premedication prior to lumbar puncture or MRI procedures is permitted during the study; however, use of benzodiazepines or other sedatives is not permitted within 2 days or 5 half-lives (whichever is longer) prior to any COA. 3. Any stimulant medication (eg, amphetamine, dextroamphetamine, dexmethylphenidate, lisdexamfetamine, methylphenidate) is prohibited unless prescribed as a stable regimen for at least 90 days prior to the first study treatment administration on Part 1. Stimulant medications should not be initiated during the study. 4. Any sedatives, with the exception of sedatives used during the imaging procedure, are prohibited unless prescribed as a stable regimen for at least 90 days prior to the first study treatment administration and the dose should be kept as stable as possible during the study. All changes should be captured in the electronic case report form (eCRF). Antidepressants are allowed when prescribed as a stable regimen for at least 90 days prior to the first study treatment administration, or if started after randomization and maintained at a stable dose. 5. Any passive immunotherapy (immunoglobulin) or other long-acting biologic agent that is under evaluation to prevent or postpone cognitive decline within 1 year of Screening for Part 1. 6. Any exposure to an anti-sortilin antibody prior to enrollment in Part 1; use of any experimental oral therapy, biologic therapy, or any other investigational treatment within 90 days or 5 half-lives prior to the first study treatment administration on Part 1, whichever is longer. 7. Any experimental vaccine or gene therapy; routinely recommended vaccinations are allowed, as well as any vaccine against SARS-CoV-2. 8. Typical (first-generation) antipsychotic or neuroleptic medication within 90 days prior to the first study treatment administration on Part 1, except as needed for brief treatment of a nonpsychiatric indication (eg, emesis). Use of atypical (second-generation) antipsychotic medications or use of pimavanserin is allowed during the study if treated with a stable regimen for at least 90 days prior to the first study treatment administration on Part 1. In addition, short-term use of these medications is permitted for treatment of anxiety and agitation, including study procedures. Short-term use should be

	stopped within 2 days or 5 half-lives (whichever is longer) prior to cognitive assessments. 9. Anticoagulation therapy is exclusionary for individuals that consent to lumbar puncture. Note: Use of aspirin or antiplatelet medication is allowed pre-study and during the study. 10. Systemic immunosuppressive therapy or use or anticipated systemic immunosuppressive therapy use during the study. a. Use of prednisone ≤10 mg/day or an equivalent corticosteroid is allowed during the study if treated with a stable regimen for at least 90 days prior to the first study treatment administration on Part 1, and participant has hemoglobin >9 g/dL, WBC count >3,000/mm^3, absolute neutrophil count >1,000/mm^3, and platelet count >100,000/mm^3. b. Treatment with steroids for acute exacerbations of asthma, chronic obstructive pulmonary disease (COPD), or flares of autoimmune conditions like Rheumatoid Arthritis is allowed for short-term use (eg, 10 days for asthma). 11. Chronic use of opioids (including long-acting opioid medication) within 30 days prior to the first study treatment administration on Part 1. a. Intermittent short-term use (<1 week) of opioid medications for pain is permitted pre-study and during the study, except within 2 days or 5 half-lives (whichever is longer) prior to any COA.
Efficacy Clinical Outcome Assessments (COAs):	COAs include the following: • Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center frontotemporal lobar degeneration Behavior and Language Domains (CDR® plus NACC FTLD) • Clinical Global Impression-Severity (CGI-S) • Frontotemporal Dementia Rating Scale (FRS) • Clinical Global Impression-Improvement (CGI-I) • Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
Quality of Life COAs	• European Quality of Life-5 Dimensions (EQ-5D) • Zarit Burden Interview (ZBI)
Pharmacoeconomic COAs	• Resource Utilization in Dementia-Lite Version (RUD-Lite)
Exploratory COAs	• Winterlight Labs Speech Assessments (for participants who agree to participate in these optional assessments only)
Safety Assessments:	Safety assessments include monitoring AEs; physical examinations; neurological examinations; vital signs and weight; ECGs; MRIs; clinical laboratory analyses in blood and urine; suicidality assessments; and ADAs throughout the study.

Pharmacodynamic and Disease Biomarker Assessments:	PD and disease biomarker assessments include the following: • Blood-based biomarkers (blood plasma samples for progranulin protein [PGRN] and blood serum samples for NfL levels) • Imaging biomarkers: global and regional brain volumes, volume of white matter hyperintensities (measured by volumetric MRI); brain perfusion (measured by arterial spin labeling MRI); and fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity (measured by diffusion-tensor imaging) • Part 1 only: Optional CSF-based biomarkers (for PGRN and NfL)
Pharmacokinetic Assessments:	Blood and optional CSF samples will be collected throughout Part 1 to measure AL001 concentrations. Blood samples will be collected throughout Part 2 to measure AL001 concentrations.
Study Treatment, Dosage, and Route of Administration:	**Part 1 (Double-Blind, Placebo-Controlled Treatment Period)** All participants will receive IV AL001 (60 mg/kg) or placebo over approximately 60 minutes on Day 0 and then q4w for a total of 25 doses over a 96-week period. Study treatment administration on Day 0 will not occur until all baseline assessments are completed. **Part 2 (Optional OLE)** Participants in the OLE will receive open-label AL001 60 mg/kg IV over approximately 60 minutes q4w. An individual participant may continue to receive AL001 on the OLE portion of the study for up to 25 additional doses over a 96-week dosing period, or until commercial availability of AL001 in the country where the participant is being treated, whichever is earlier.
Sample Size:	The study was designed to enroll both symptomatic participants with a CDR® plus NACC FTLD-SB score >0.5 and pre-symptomatic/at-risk participants with a CDR® plus NACC FTLD-SB score ≤0.5 with an elevated serum NfL. At the initial design stage of the trial, data from the Genetic FTD Initiative (GENFI) registry were analyzed to obtain an estimate of the expected change over time in the clinical co-primary endpoint CDR plus NACC FLTD-SB, and its associated variability, in the at-risk and symptomatic participants for the purpose of sample size estimation. This analysis showed the 2-year coefficient of variation (CV) for the change in the CDR® plus NACC FLTD-SB was 77% for the symptomatic cohort and 165% for the at-risk cohort. Following a recommendation from the FDA during the review of the draft AL001-3 SAP, the study objective was changed to include plasma PGRN as a biomarker co-primary endpoint. As a result of this change, a post hoc power calculation was performed to ensure that there was still sufficient power for this study to support the inclusion of plasma PGRN as a co-primary endpoint. Based on available data from AL001-2 for symptomatic FTD-*GRN* participants treated with AL001, it is expected that after 96 weeks of treatment, participants would experience a mean (SD) of the change from baseline of log-10 transformed plasma PGRN concentration of 0.45 (0.0815). Based on longitudinal data from a large observational cohort of FTD patients (Sellami 2020), plasma PGRN levels are low and stable throughout the course of the disease up to 10 years following disease onset. As a result, plasma PGRN levels are not expected to change over 96 weeks while on placebo. Therefore, the change from baseline of log-10 transformed plasma PGRN concentration for the placebo arm is assumed to be 0, with a common SD of 0.0815 to match the AL001-treated participants. Anticipating that there may be as many as 63 participants with a baseline and week 96 plasma PGRN concentration, in a 2:3 allocation ratio of placebo:AL001, a two-sample t-test shows that there is >99% power at a 1-sided 2.5% significance level to detect the treatment difference. Therefore, there is adequate power in this study to detect a

	treatment effect on both the clinical co-primary endpoint and the biomarker co-primary endpoint. Based on the small number of at-risk participants who have enrolled and routine blinded monitoring of the accumulating INFRONT-3 data, which has indicated a lack of progression in the at-risk participants thus far, the primary analysis population was changed to focus on the symptomatic participants. It is estimated that for a primary analysis based on the symptomatic population only, 90 participants would be required to achieve at least 85% power (with 1-sided 2.5% significance level) to detect a 40% slowing in the AL001 treatment group, relative to the placebo group, assuming the 96 weeks CV is 65% and the 48- and 96-week dropout rates are 30% and 40%, respectively. The new proposed sample size (N=90 symptomatic participants) is based on the observed 2-year variability (CV=68%) from the GENFI and FTD research consortium consisting of Advancing Research and Treatment in Frontotemporal Lobar Degeneration and Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (ALLFTD) registries reported by Staffaroni (Staffaroni 2022). A slightly smaller variability (65%) has also been assumed due to routine blinded monitoring of the accumulating INFRONT-3 data.
Statistical Methods:	The primary analysis will use symptomatic participants in the full analysis set (FAS-symptomatic), and include all data collected on these participants during the trial, irrespective of whether a participant discontinues study treatment or took a prohibited medication. This is aligned to an estimand based on the Treatment Policy strategy for discontinuations from treatment/use of other prohibited medications. The trial has been designed to follow all participants randomized, irrespective of whether they discontinue study treatment, and collect all COA assessments until Part 1/Part 2 EOS or Safety Follow-up visit, whichever is later. The primary analysis for the clinical co-primary and all secondary endpoints will use a proportional mixed model for repeated measures (pMMRM) approach (Wang 2022). A pMMRM models the treatment effect as a single proportional difference at each post-baseline visit. Because greater noise than signal is expected in the early stages of the trial, the pMMRM model will only assume the treatment effect is proportional from Week 48 through Week 96, and use the time points of Week 48, 72, and 96 to estimate the treatment effect (θ). The following superiority hypothesis will be tested using a 1-sided 2.5% significance level: • H0 (null): $\theta \leq 0$, indicating that treatment does not slow disease progression relative to placebo control. • H1 (alternative): $\theta > 0$, indicating that treatment slows disease progression relative to placebo control. The primary analysis for the biomarker co-primary (plasma PGRN) and all other exploratory biomarker endpoints will use a mixed model for repeated measures (MMRM) to compare the difference between treatment and placebo group in change from baseline of the log-10 transformed values at Weeks 96. The hypothesis to be tested for the biomarker co-primary and exploratory fluid biomarker endpoints (modeling the log-10 transformed values) will be tested using a 1-sided 2.5% significance level as follows: • H0 (null): $\Delta = 0$, indicating that the change from baseline at Week 96 in treatment group is the same as that of the placebo group. • H1 (alternative): $\Delta > 0$ for plasma PGRN, or $\Delta < 0$ for serum NfL, indicating a treatment benefit favoring the AL001.

	Interpretation of inferential analyses and adjustments for multiplicity for secondary endpoints will only be made if success is declared for both co-primary endpoints analyses. If the primary hypothesis for both primary endpoints is rejected at the one-sided 0.025 significance level, the remaining endpoints will be tested in sequential order: CGI-S, FRS, CGI-I and RBANS.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Antidrug antibody
ADRs	Adverse drug reactions
AE	Adverse event
AL001	Alector company code for latozinemab
ALLFTD	FTD research consortium consisting of Advancing Research and Treatment in Frontotemporal Lobar Degeneration (ARTFL) and Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS)
ALS	Amyotrophic lateral sclerosis
ALT	Alanine aminotransferase
ATC	Anatomical therapeutics chemical class
AST	Aspartate aminotransferase
AUC_{ss}	Area under the concentration-time curve at steady state
BP	Blood pressure
bvFTD	Behavioral variant frontotemporal dementia
CDR®	Clinical Dementia Rating Scale
CDR® plus NACC FTLD	Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center frontotemporal lobar degeneration Behavior and Language Domains
CDR® plus NACC FTLD-SB	Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center frontotemporal lobar degeneration Behavior and Language Domains Sum of Boxes
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
cGMP	Current Good Manufacturing Practice
CI	Confidence interval
C_{max}	Maximum observed concentration
CNS	Central nervous system
COA	Clinical outcome assessment
COPD	Chronic obstructive pulmonary disease
CRO	Clinical research organization / Contract research organization
CSF	Cerebrospinal fluid
CSR	Clinical study report
C_{trough}	Trough concentration
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOS	End of Study

Abbreviation	Definition
EOT	End of Treatment
EQ-5D	European Quality of Life-5 Dimensions
FAS	Full analysis set
FDA	Food and Drug Administration
FIH	First-in-human
FRS	Frontotemporal Dementia Rating Scale
FTD	Frontotemporal dementia
FTD-*GRN*	Frontotemporal dementia with heterozygous progranulin gene mutations
FTLD	Frontotemporal lobar degeneration
GENFI	Genetic FTD Initiative
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GRN	Progranulin gene
HV	Healthy volunteers
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
iDMC	Independent Data Monitoring Committee
IEC	Independent ethics committee
IgG1	Immunoglobulin G1
IL-6	Interleukin 6
IP	Investigational product
IRB	Institutional review board
IRT	Interactive response technology
IV	Intravenous(ly)
MDRD	Modification of Diet in Renal Disease
MMRM	Mixed Effect Model of Repeated Measures
MRI	Magnetic resonance imaging
NIA GUID	National Institute of Aging Global Unique Identifier
Nf	Neurofilament
NfL	Neurofilament light chain
NONMEM	Nonlinear Mixed Effects Modelling
OLE	Open-label extension
PD	Pharmacodynamic(s)
PE	Physical examination

Abbreviation	Definition
PGRN	Progranulin protein
PK	Pharmacokinetic(s)
pMMRM	Proportional Mixed Effect Model of Repeated Measures
PPA	Primary progressive aphasia
PPS	Per-Protocol Analysis Set
PT	Preferred Term
q4w	Every 4 weeks
QTcF	Fridericia's correction of QT interval
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
REM	Rapid eye movement
RUD-Lite	Resource Utilization in Dementia-Lite version
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard deviation
Sheehan-STS	Sheehan-Suicidality Tracking Scale
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TDP-43	Transactive response DNA-binding protein of 43 kD
TEAE	Treatment-emergent adverse event
TMF	Trial Master File
ULN	Upper limit of normal
US	United States
USA	United States of America
WBC	White blood cell
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
WLA	Winterlight Labs Speech Assessment
WOCBP	Woman of childbearing potential
ZBI	Zarit Burden Interview

1. BACKGROUND INFORMATION

1.1. Introduction

1.1.1. Frontotemporal Dementia

Frontotemporal lobar degeneration (FTLD) or frontotemporal dementia (FTD) is a pathologically and clinically heterogenous neurodegenerative syndrome characterized by progressive decline in behavior, language, executive skills, and motor function with atrophy in the frontal and temporal lobes (Rabinovici 2010). Classifications of FTD are based on genotype, brain pathology, and phenotype. It is a rare disease with a current estimated prevalence of 60,000 persons in the United States (US), and in Europe estimates for FTD range from 4 to 17 people per 100,000 in the population (Onyike 2013). FTD progresses rapidly with survival after symptom onset of 3 to 14 years (Onyike 2013).

Individuals with FTD can present with various clinical symptoms, including marked changes in personality, speech, or executive function, which can make obtaining an accurate diagnosis challenging. Behavioral variant FTD (bvFTD) is characterized by changes in personality and behavior, with persons displaying a mixture of apathy, disinhibition, and lack of insight. Primary progressive aphasia (PPA) is characterized by a gradual, progressive impairment of language capabilities. The 2 principal language variants, progressive nonfluent aphasia and semantic dementia, present with impaired speech production or impaired comprehension of grammar (agrammatism) and semantic memory, respectively. These progressive changes result in disrupted relationships with family and friends, loss of decision-making ability and future planning, memory impairment, and loss of independence (Tatton 2014).

1.1.2. Frontotemporal Lobar Degeneration, *GRN*

Frontotemporal lobar degeneration can be broadly split into 3 principal pathology categories, based on manifest nuclear and cytoplasmic inclusions: (1) FTLD-TDP, with neuronal and glial inclusions immunoreactive for transactive response DNA-binding protein of 43 kD (TDP-43); (2) FTLD-tau, with tau-positive inclusions containing fibrillar, hyperphosphorylated tau; and (3) a small number of tau-negative, TDP-43 negative cases that are immunoreactive to the fused in sarcoma protein (Perry 2017; Mann 2017). TDP-43 pathology is seen in most FTD cases caused by a genetic mutation and is identified in up to 50% of FTD patients overall (Ng 2015).

A family history is present in 20% to 40% of FTD cases, and 10% of FTD cases are inherited in an autosomal dominant pattern (Rohlfing 2017). Progranulin gene (*GRN*) mutations account for up to 20% of all familial FTD cases and are caused by a loss-of-function mutation in 1 allele of *GRN* (Gass 2006; Rademakers 2012; Rohlfing 2017; Cruts 2012). Heterozygous loss-of-function *GRN* deficiency almost invariably leads to development of FTD, making *GRN* a causal gene for the disease (Boxer 2013a; Boxer 2013b).

GRN mutations include over 77 different mutations in more than 240 unrelated families, which accounts for up to 16% of families worldwide carrying a neurodegenerative disease-causing mutation (Ghidoni 2012) that encodes for the secreted glycoprotein progranulin (PGRN) (Rademakers 2012). Frontotemporal dementia patients carrying this mutation have a >50% reduction in plasma and cerebrospinal fluid (CSF) levels of this secreted protein (Meeter 2016b). PGRN is associated with many cellular processes that include, but are not limited to,

embryogenesis, inflammation, wound repair, neurodegeneration, and lysosome function (Chitramuthu 2017). In the brain, PGRN promotes neurite outgrowth (Gass 2012) and enhances the survival of motor and cortical neurons (De Muynck 2013). The predominant clinical presentation of *GRN* mutation patients is bvFTD or PPA.

1.1.3. Sortilin and AL001

Human and mouse genetic studies identified the transmembrane receptor sortilin, encoded by the *SORT1* gene, as the major regulator of PGRN levels in plasma and the brain (Hu 2010; Carrasquillo 2010). Sortilin binds PGRN and targets it for lysosomal degradation, resulting in a reduction of extracellular PGRN. Blocking sortilin/PGRN interactions, therefore, provides a therapeutic strategy for sustaining PGRN levels in the central nervous system (CNS) and minimizing progression of FTD-associated dementia.

AL001 (latozinemab), a recombinant monoclonal antibody that binds specifically to sortilin, increases or normalizes PGRN levels in plasma and CSF, and has the potential to be efficacious in carriers of heterozygous loss-of-function *GRN* mutations causative of FTD.

AL001 is currently in development and does not have marketing authorization. The European Medicines Agency (EMA) adopted the decision to grant a full pediatric product specific waiver for the treatment of FTD on 11 Aug 2021 (EMEA-002997-PIP01-21).

1.1.4. Neurofilament Light Chain

Neurofilaments (Nf) are highly specific major structural proteins of axons, which predominantly consist of Nf-light chain (NfL), Nf-medium chain, Nf-heavy chain, and alpha-internexin. Neurofilament levels are significantly elevated following neuronal degeneration, as disruption of axonal membranes releases Nf into the interstitial fluid and eventually into CSF and blood. Due to this relationship, blood Nf levels may be an effective tool for predicting and monitoring disease progression and for measuring efficacy of investigative neuroprotective treatments (Gaiottino 2013).

Increased NfL levels have been observed in FTD (Rohrer 2016). A study in 174 participants identified NfL in both serum and CSF as a potential biomarker for FTD onset (Meeter 2016a). Cerebrospinal fluid NfL levels in symptomatic carriers were significantly elevated compared to those in pre-symptomatic carriers; serum NfL was elevated in FTD patients as well and correlated highly with CSF NfL. In addition, in bvFTD patients' serum, NfL is correlated with their functional clinical scores and with atrophy of several brain regions, including the frontal lobes and the white matter underlying these lobes (Steinacker 2018). In addition, Rojas-Martinez et al, found that an elevated serum NfL level predicts clinical progression (Rojas-Martinez 2019) and may be used as an enrichment strategy to identify participants at risk for developing symptoms of FTD.

1.2. Findings from Nonclinical and Clinical Studies

1.2.1. Nonclinical Studies

Results from nonclinical pharmacology studies of AL001 were consistent with the proposed mechanism of sortilin blocking and subsequent increase in PGRN levels. The toxicology of AL001 was evaluated via single- and repeat-dose preliminary and Good Laboratory Practice

(GLP) repeat-dose (4-week and 26-week) intravenous (IV) toxicology studies in cynomolgus monkeys. Across all the dose levels assessed (up to 200 mg/kg), there were no significant toxicology findings in the nonclinical studies.

Refer to the AL001 Investigator's Brochure (IB) for additional details regarding nonclinical pharmacology, pharmacokinetics (PK), and toxicology data.

1.2.2. Clinical Studies

1.2.2.1. Study AL001-1 (Completed)

Study AL001-1 was a first-in-human (FIH) Phase 1 study that assessed the safety, tolerability, PK, and pharmacodynamics (PD) of AL001 in healthy volunteers (HV) and carriers of *GRN* mutations causative of FTD. The study was conducted in 2 parts.

Part 1, Healthy Volunteers

The first part of this study evaluated the effect of single doses of AL001 ranging from 2 mg/kg to 60 mg/kg in HV to identify the safest maximum dose and explore PK and PD in plasma and CSF. A total of 50 HV were enrolled: 42 participants in 5 randomized single ascending dose cohorts (Cohorts 1 through 5) with increasing dose levels of AL001 (or placebo) ranging from 2 mg/kg to 60 mg/kg via IV administration, plus 8 participants in the single-dose 60 mg/kg expansion cohort (Cohort 6).

Plasma PGRN Concentrations: Administration of AL001 to HV at single doses of 2 mg/kg, 6 mg/kg, 15 mg/kg, 30 mg/kg, and 60 mg/kg caused dose-dependent peripheral increases in plasma PGRN levels; the elevations of PGRN levels were sustained for a longer duration at the highest dose levels. Maximum concentrations of PGRN were measured 5 to 12 days after the infusion. At the 30 mg/kg dose, plasma PGRN concentrations remained elevated at more than twice the baseline level from 2 days after dosing to 29 days after dosing. At the 60 mg/kg dose, plasma PGRN concentrations remained elevated at more than twice the baseline level from 2 days after dosing to more than 29 days after dosing. The maximum percent change from baseline was statistically significant compared to pooled placebo for each of the HV dose cohorts and ranged from 2.29 (2 mg/kg) to 3.14-fold (60 mg/kg) over baseline. CSF samples were collected from HV in the 15 mg/kg, 30 mg/kg, and 60 mg/kg dose cohorts before dosing and approximately 30 hours (Day 2) and 12 days (Day 13) after dosing.

CSF PGRN Concentrations: A statistically significant increase in CSF PGRN levels (compared to baseline) was seen at both post-dose time points for each of these 3 cohorts. The maximum increase in CSF PGRN was observed 12 days after dosing: 1.57 times for 15 mg/kg, 1.84 times for 30 mg/kg, and 2.11 times for 60 mg/kg compared to baseline. No statistically significant changes in CSF PGRN levels were observed in participants who received placebo. In the 60 mg/kg expansion cohort, 24 days after dosing, the PGRN level was increased 1.83-fold over baseline, and 42 days after dosing the PGRN level was increased 1.23-fold over baseline. Coefficients of variation were in the range of 20% to 40% for the 30 mg/kg and 60 mg/kg cohorts over the sampling period.

Safety: AL001 was generally well tolerated through the highest dose assessed (60 mg/kg), without dose-limiting toxicities or apparent trends in adverse events (AEs).

Part 2, Participants with Asymptomatic FTD-*GRN* or Symptomatic FTD-*GRN*

The second part of the study was conducted in 2 cohorts: the first cohort assessed safety, PK, and PD after a single dose of AL001 in asymptomatic carriers of a loss-of-function *GRN* mutation causative of FTD (asymptomatic FTD-*GRN*); while the second cohort assessed safety, PK, and PD after repeated dosing in symptomatic FTD carriers of a loss-of-function (symptomatic FTD-*GRN*). A total of 6 asymptomatic FTD-*GRN* participants and 8 symptomatic FTD-*GRN* participants were enrolled and completed dosing in the second part of the study. Asymptomatic FTD-*GRN* participants were administered a single IV dose of AL001 at 60 mg/kg and symptomatic FTD-*GRN* participants were administered 3 doses of IV AL001 30 mg/kg, every 2 weeks.

Plasma PGRN Concentrations: Consistent with the literature (Meeter 2016b), both the asymptomatic FTD-*GRN* cohort (N=5 who received 60 mg/kg) and the symptomatic FTD-*GRN* cohort (N=8) had substantially lower baseline plasma PGRN concentrations than HV cohorts (one asymptomatic participant was incorrectly dosed and is not included in the summary PD analyses). Mean baseline plasma PGRN concentration for the asymptomatic FTD-*GRN* cohort was 32.6 ng/mL (standard deviation [SD] of 13.6); for the symptomatic FTD-*GRN* cohort, mean baseline plasma PGRN concentration was 31.7 ng/mL (SD of 12.7). Treatment of the asymptomatic FTD-*GRN* cohort with a single dose of 60 mg/kg AL001 resulted in an increase of plasma PGRN to approximately the baseline level of HV for 24 days (median concentrations of 118 to 124 ng/mL at Day 6 through Day 30 of the study). Treatment of the symptomatic FTD-*GRN* cohort with 3 doses of 30 mg/kg AL001 over a 4-week period resulted in an increase of plasma PGRN to at least 80% of the baseline level of HV for approximately 49 days, beginning 7 days after the first dose (median concentrations of 93.7 to 97.6 ng/mL at Day 8 through Day 57 of the study).

CSF PGRN Concentrations: Parallel to the results observed for plasma concentrations of PGRN, both the asymptomatic FTD-*GRN* cohort (N=5 who received 60 mg/kg) and the symptomatic FTD-*GRN* cohort (N=8) had substantially lower baseline PGRN concentrations in CSF than HV cohorts (mean of 1.67 ng/mL for the asymptomatic FTD-*GRN* cohort, 1.82 ng/mL for the symptomatic FTD-*GRN* cohort; approximately 55% to 58% of the HV mean of 3.1 ng/mL). Treatment of the asymptomatic FTD-*GRN* cohort with a single dose of 60 mg/kg AL001 resulted in an increase of PGRN in CSF to 3.76 ng/mL, approximately 1.2 times the baseline level of HV, assessed 12 days after dosing. Treatment of the symptomatic FTD-*GRN* cohort with 3 doses of 30 mg/kg AL001 over a 4-week period resulted in an increase of PGRN in CSF to 3.76 ng/mL, approximately 1.2 times the baseline level of HV, assessed 28 days after the third dose of 30 mg/kg AL001 (57 days after the initial dose).

Safety: There were no deaths, no AL001-related serious adverse events (SAEs), and no dose-limiting AEs. AEs were predominantly mild to moderate in severity.

1.2.2.2. Study AL001-2 (Ongoing)

Study AL001-2 is an ongoing Phase 2, multicenter, open-label study evaluating the long-term safety profile of AL001 in heterozygous carriers of *GRN* or *C9orf72* mutations causative of FTD. The study has 2 parts. During Part 1 (Treatment Period), participants receive open-label treatment with 60 mg/kg IV AL001 administered every 4 weeks (q4w) for 96 weeks. Part 2 is an

optional open-label extension (OLE) to assess long-term (up to 96 weeks extended treatment period) safety and tolerability in participants who complete the Part 1 96-week treatment period.

Enrollment in Part 1 of this study was initiated in the third quarter of 2019 and the first participant was dosed on 27 Sep 2019. Enrollment in the study was completed in Feb 2022, with a total of 33 participants exposed to AL001 in Study AL001-2. Participation is ongoing as of the date of this protocol.

Refer to the AL001 IB for additional details on safety events in ongoing clinical studies.

1.2.3. Known and Potential Risks and Benefits

Refer to the AL001 IB for detailed information on the safety profile of AL001.

1.2.3.1. Known Risks of the Drug Class

Immune Response: Monoclonal antibodies like AL001 may be associated with a potential immune response, such as hypersensitivity or hypersensitivity-like reactions, including severe anaphylactic reactions.

1.2.3.2. Risks of AL001

Risks Associated with AL001 Study Procedures and Assessments: The study procedures and assessments to be performed are not considered to be of great burden to participants and are not associated with high risk.

Important Identified Risks: There are no important identified risks for AL001.

Serious Adverse Drug Reactions: No serious adverse drug reactions (ADRs) have been identified in Study AL001-1, Study AL001-2, or Study AL001-3 (blinded data). There are no expected serious ADRs for AL001.

Immunogenicity: Participants treated with AL001 have developed antidrug antibodies (ADAs). The preliminary assessment of ADAs has not identified any associations between incident ADAs with PK, PD, or clinical safety in participants receiving single-dose AL001 or 3 doses of AL001 administered every 2 weeks. Based on the current information from studies with AL001, the impact of immunogenicity on AL001 exposure, PD effects, and clinical safety do not appear consequential with short duration of exposure. However, the impact of ADAs continues to be assessed in ongoing AL001 clinical studies with longer-term exposure. See the AL001 IB for more information on immunogenicity.

Adverse Events: AL001 has been generally well tolerated. There have been no treatment-related deaths, no treatment-related SAEs, and no treatment-related AEs leading to study discontinuation in any study. One treatment-emergent adverse event (TEAE; [redacted] AEs have been predominantly mild to moderate in severity. Refer to the AL001 IB for a detailed summary of AEs.

Summary of Adverse Events - Study AL001-1 (completed): Clinical data are available from the completed FIH study, Study AL001-1. A total of 52 participants received AL001 and 12 participants received placebo. The participants had a mean age of 43.6 years (range 19-71 years). There were no deaths and no dose-limiting AEs. There was no higher incidence of

TEAEs with AL001 treatment than with placebo, and the incidence of TEAEs was similar across all AL001 dosing regimens and between the HV and FTD-*GRN* cohorts. There were no dose-related trends in TEAEs.

The most frequent TEAEs were post-lumbar puncture syndrome (ie, headache after lumbar puncture), headache, puncture site pain, anemia, lipase increased, myalgia, vomiting, and upper respiratory tract infection. There were 2 potentially life-threatening SAEs reported as unrelated to AL001 in the HV cohorts: 1 event of [redacted] occurring in the pooled placebo cohort (attributed to [redacted] in a participant occurring [redacted] weeks after receiving placebo), and 1 event of [redacted] occurring in the SD 60 mg/kg AL001 HV cohort (attributed to [redacted] in a participant occurring [redacted] weeks after receiving AL001). All other TEAEs were mild or moderate in severity and generally resolved.

Interim Safety Results - Study AL001-2 (ongoing): As of the 27 Aug 2022 data cutoff date for IB Version 7.0, a total of 33 participants had been exposed to AL001 in Study AL001-2; 23 were ongoing and 2 had completed study drug treatment as of the data cutoff date. Eight participants have discontinued the study: 5 participants withdrew consent, 1 participant discontinued due to a TEAE not related to study treatment, 1 participant was discontinued at the Investigator's discretion, and 1 participant discontinued for an administrative or other reason. The mean age of participants as of the data cutoff was 60.3 years (range 32 to 78 years).

AL001 has been generally well tolerated in this study. As of the data cutoff, there were 185 TEAEs in 31 participants (5 participants in asymptomatic FTD-GRN, 11 participants in symptomatic FTD-GRN, and 15 participants in symptomatic FTD-C9orf72 cohorts). The TEAEs have been predominantly mild in severity. There has been 1 unrelated death due to [redacted], described further below.

The most frequently reported TEAEs (≥10%) across the total safety population were fall (16 events in 13 participants; 39.4%), urinary tract infection (11 events in 8 participants; 24.2%), coronavirus disease (COVID-19; 5 events in 5 participants; 15.2%), and rash and headache (both 4 events in 4 participants; 12.1%). All other TEAEs were reported in 3 or fewer participants.

Five participants had TEAEs that were associated with treatment interruption. The participant that had [redacted] pneumothorax [redacted] (mentioned below) also had a treatment interruption due to these TEAEs and a TEAE of [redacted] considered not related to study drug. Following review of the participant's medical history by the Medical Monitor, the participant was later discontinued from the study. One participant in the [redacted] cohort had [redacted] of mild severity (without associated AEs) that was considered by the Investigator to be related to study drug and led to study drug interruption. One participant in the [redacted] cohort had [redacted] of moderate severity considered not related to study drug, but which also led to treatment interruption. One participant in the [redacted] cohort had moderate [redacted] which was considered related to study drug. Study treatment was interrupted, [redacted] and study treatment was restarted. The event resolved. One participant in the FTD-*GRN* cohort had [redacted] of mild severity and mild [redacted] which were both considered

related to study drug. Study treatment was interrupted. As of the date of data cutoff (27 Aug 2022; 226 days after the last treatment), the events were not resolved.

There have been 6 SAEs reported by 5 participants, all considered unrelated to study treatment, including 1 unrelated death due to muscle weakness.

- There was 1 severe SAE of [redacted] reported that occurred in a [redacted]-year-old [redacted] participant from the [redacted]. [redacted] The event was considered unrelated to study treatment and study treatment was discontinued at the Investigator's discretion as the participant had initiated treatment with a prohibited medication.
- There was 1 event of [redacted] reported in a [redacted]-year-old [redacted] participant. The event was assessed as not related to study treatment and study drug was interrupted due to the SAE. The event was reported as a complication from [redacted] surgery for [redacted] The event was reported as recovered/resolved. The participant was discontinued from study for administrative or other reasons, as this participant no longer met inclusion/exclusion criteria due to [redacted] conditions.
- There was 1 event of [redacted] reported for a [redacted]-year-old [redacted] participant. The event was assessed as not related to study treatment and study drug dose was not changed due to the event. Causality was considered likely related to underlying FTD, [redacted], and administration of [redacted]. The event was reported as recovered/resolved. The study treatment was withdrawn due to disease progression.
- There was 1 severe SAE of [redacted] that occurred in a [redacted]-year-old [redacted] participant with [redacted] on Study Day [redacted]. The event was assessed as not related to study treatment and study drug was withdrawn. Causality of the event was likely related to the underlying disease of [redacted] rather than AL001. Outcome of the event is not resolved.
- There was 1 fatal event of [redacted] and 1 [redacted] reported for a [redacted]-year-old [redacted] participant with [redacted]. The event of [redacted] was reported on Study Day [redacted] and was assessed as not related to study treatment and study treatment dose was not changed. Causality was likely related to the participant's underlying FTD. The participant's concomitant medications of [redacted]. Outcome of the event was resolved. This participant also experienced the subsequent fatal SAE of [redacted] on Study Day [redacted] which was assessed as not related to study treatment. The participant had received [redacted]. The participant developed [redacted], including [redacted] Action taken with study treatment was not applicable. Alector considers the event of [redacted] to be confounded by the participant's history of [redacted] resulting in the fatal outcome.

1.2.3.3. Potential Benefits of AL001

The AL001 clinical development program is focusing on interventions that increase PGRN concentration in the blood and CSF. AL001 offers an innovative potential treatment for carriers of *GRN* mutations causative of FTD. AL001 binds specifically to human sortilin and increases PGRN levels by blocking its degradation. The Phase 1 study demonstrated target engagement in HV, asymptomatic carriers, and symptomatic patients with *GRN* mutations; longitudinal plasma and CSF collections show a dose-dependent and long-lasting increase in PGRN levels. AL001 represents a promising therapeutic strategy by rescuing *GRN* haploinsufficiency for familial forms of FTD due to mutations in *GRN,* not only in patients with FTD, but also in at-risk individuals.

1.2.3.4. Benefit/Risk Assessment for AL001-3 Study Participants

FTD is a rare, early-onset form of dementia that progresses rapidly, with survival after symptom onset of 3 to 14 years (Onyike 2013). There are currently no approved treatments for FTD (Boxer 2013a; Boxer 2013b). Participation in Study AL001-3 offers the possibility of receiving AL001, a novel investigational recombinant human monoclonal immunoglobulin G1 (IgG1) antibody that blocks sortilin, for the treatment of adults at risk for or with FTD due to a mutation in the *GRN* that leads to lower levels of PGRN. By blocking sortilin, decreasing the rate of PGRN clearance, and therefore raising the concentration of PGRN, AL001 may decrease the rate of neurodegeneration and clinical decline associated with FTD among patients who carry *GRN* mutations. In Part 1 of the study, participants will be randomly assigned to either AL001 or placebo. In Part 2 of the study (Optional OLE), eligible participants from Part 1 may receive open-label AL001.

More detailed information about the known and expected benefits and risks of AL001 is described in the AL001 IB.

The safety profile of AL001 for participants in this study is described in Section 1.3.2, with further guidance for investigators provided in the AL001 IB. Any risks to participants in Study AL001-3 will be minimized through a combination of screening for appropriate eligibility criteria (see Section 4) and rigorous safety monitoring to mitigate risks and careful toxicity management (see Section 6.5, Section 7, and AL001 IB). AE and/or SAE collection will occur up to 10 weeks after the last dose of study treatment. Frequent safety monitoring will ensure that updated safety information is available in a timely manner and that any future changes to the benefit-risk profile of AL001 are appropriately reported and managed. An independent data monitoring committee (iDMC) with the capability of reviewing unblinded data during Part 1 of the study will provide additional oversight of the study supplementing the Sponsor's careful screening, diligent monitoring, and management of participant safety.

Taking the available data on the investigational therapy, together with the study design and conduct, treatment with AL001 is anticipated to be generally well tolerated and is expected to provide pharmacological effect at the dose of 60 mg/kg being administered. Participants, regardless of the treatment group to which they are randomly assigned, will receive close medical monitoring and care from qualified professionals throughout their participation in the study. The assessment procedures included in the clinical studies are not considered to be of great burden to participants and are not associated with high risk. Informed consent processes are intended to both (1) describe these potential benefits and potential risks from participating in the

study and (2) ensure, in accordance with local regulation, that a legally authorized representative is identified for participants who may not have legal capacity to provide consent, as described in Section 10.3 of the protocol. Therefore, it is plausible to conclude that the anticipated benefits of participating in this study outweigh the potential risks or inconveniences.

1.3. Rationale for the Study

1.3.1. Rationale for the Study Design

In this Phase 3 study, eligible participants at risk for or with FTD due to heterozygous loss-of-function mutations in *GRN* will each receive either IV AL001 (60 mg/kg) or placebo. The AL001 dose was determined based on the Phase 1 study results (Study AL001-1). In the single ascending dose part of Study AL001-1, a total of 50 HV within 6 dose cohorts were enrolled in the study and received single doses of AL001 ranging from 2 mg/kg to 60 mg/kg. AL001 was generally well tolerated through the highest dose assessed (60 mg/kg) without dose-limiting toxicities or apparent trends in AEs; PD assessments of PGRN changes in blood and CSF levels showed increases over baseline in all HV administered a single IV dose of AL001. After review of the safety and PK data, the second part of the study enrolled asymptomatic FTD-*GRN* participants to receive a single dose of 60 mg/kg AL001 via IV and symptomatic FTD-*GRN* participants to receive 3 doses of IV 30 mg/kg AL001 every 2 weeks. Data show that AL001 elicited a dose-dependent increase in PGRN levels in both plasma and CSF of all FTD-*GRN* participants.

FTD patients were not involved in the design of this study.

1.3.2. Rationale for Dose Selection

Phase 1 PK data (AL001 serum concentrations and CSF concentrations) were incorporated into a 3 compartment PK/PD model (Nonlinear Mixed Effects Modelling [NONMEM] v7.4) including a central compartment, a peripheral compartment, and a CSF compartment. White blood cell sortilin expression, plasma PGRN, and CSF PGRN were included, using appropriate models for elimination/degradation of these 3 biomarkers. Data from all HV cohorts (2, 6, 15, 30, and 60 mg/kg) were included, in general up to 113 days post-dose (up to 42 days post-dose for CSF). Data were included for asymptomatic carriers administered a single dose of 60 mg/kg or symptomatic carriers administered 30 mg/kg every 2 weeks for a total of 3 doses. Baseline differences between HV and participants with FTD (whole blood sortilin and plasma, and CSF PGRN) were accounted for with covariates in the model. After verifying model fit to the original data, simulations of CSF PGRN from this model following repeat-dose AL001 IV administration q4w were run with robust stable, and elevated CSF PGRN levels being most clearly demonstrated at a dose level of 60 mg/kg.

1.3.3. Rationale for Treatment Duration

The treatment duration of 96 weeks in Part 1 of the study (double-blind, placebo-controlled treatment period) was chosen to facilitate a robust evaluation of the treatment effect and to allow for the possibility of latency, as well as examination of exposure/response relationships over longer intervals. The Part 1 treatment duration of 96 weeks for all participants will provide more data from all participants and it is expected that 96 weeks is sufficient duration to establish an effect in the slower-progressing participant population. At-risk participants (with a CDR® plus

NACC FTLD-SB score ≤0.5) will be required to have an elevated serum NfL level at study entry, as this level may predict clinical progression (Rojas-Martinez 2019). This enrichment strategy is being used to identify patients who may decline more rapidly and to improve the chances of observing a treatment effect during the study. The primary analysis population for both co-primary endpoints will be symptomatic participants.

The protocol includes a Part 2, optional OLE that offers an additional 96 weeks of treatment with open-label AL001 to all eligible participants who complete Part 1. Both participants who received placebo in Part 1 and those who received AL001 in Part 1 are eligible for the Part 2 OLE. The OLE will thus provide a subset of participants who will have been treated with AL001 for up to 196 weeks (50 doses) (ie, those who received blinded AL001 during Part 1 and then continued in the OLE). Participation in the OLE is optional. The optional OLE period with AL001, the first molecule shown to elevate blood and CSF progranulin levels, provides the opportunity to follow participants longitudinally for long-term safety, tolerability, and efficacy. Extension of the AL001 treatment duration is supported by the favorable safety profile of AL001 seen to date in both clinical and nonclinical studies. Treatment duration of up to 196 weeks is supported based on safety data from the chronic 26-week repeat-dose study in cynomolgus monkeys, where no AL001-related adverse findings have been observed, and based on the safety data from the FIH study (Study AL001-1) and the Phase 2 study (AL001-2).

1.4. Participant Population

This Phase 3 study will be conducted in participants at risk for or with FTD due to heterozygous loss-of-function *GRN* mutations who meet all inclusion criteria and none of the exclusion criteria. Efficacy, safety, PK, and biomarker parameters will be assessed for all participants.

2. STUDY OBJECTIVES AND ENDPOINTS

The objectives and endpoints of this study are provided in Table 1.

Table 1: Study Objectives and Endpoints

Part 1 Double-Blind, Placebo-Controlled Treatment Period: Study Objectives and Endpoints		
	Objectives	**Estimand/Endpoint**
Co-primary Efficacy	To evaluate the efficacy of AL001 compared with placebo in symptomatic participants as measured by the CDR® plus NACC FTLD-SB	**Target population:** Symptomatic carriers of a *GRN* mutation causative of FTD as defined by the inclusion and exclusion criteria.
		Variable of interest: Change from baseline to Weeks 48, 72, and 96 in the CDR® plus NACC FTLD-SB.
		Intercurrent events and corresponding strategy: Study treatment discontinuation/prohibited concomitant medications (Treatment Policy). All observed values of the variable of interest, regardless of whether or not the participant has discontinued treatment/taken a prohibited medication.
		Population-level summary variable: Percent reduction of the placebo group change from baseline across Weeks 48, 72, and 96.
Co-primary Biomarker	To evaluate the treatment effect of AL001 compared with placebo in symptomatic participants as measured by plasma PGRN concentration	**Target population:** Symptomatic carriers of a *GRN* mutation causative of FTD as defined by the inclusion and exclusion criteria.
		Variable of interest: Change from baseline of the log-10 transformed values at Week 96 in plasma PGRN concentration.
		Intercurrent events and corresponding strategy: Study treatment discontinuation/prohibited concomitant medications (Treatment Policy). All observed values of the variable of interest, regardless of whether or not the participant has discontinued treatment/taken a prohibited medication.
		Population-level summary variable: Mean change from baseline of log-10 transformed concentrations in the treatment group relative to the placebo group at Week 96.

Table 1: Study Objectives and Endpoints (Continued)

Part 1 Double-Blind, Placebo-Controlled Treatment Period: Study Objectives and Endpoints		
Secondary Efficacy	To evaluate the efficacy of AL001 compared with placebo in symptomatic participants as measured by CGI-S	**Target population:** Symptomatic carriers of a *GRN* mutation causative of FTD as defined by the inclusion and exclusion criteria.
		Variable of interest: Change from baseline to Weeks 48, 72, and 96 on the CGI-S.
		Intercurrent events and corresponding strategy: Study treatment discontinuation/prohibited concomitant medications (Treatment Policy). All observed values of the variable of interest, regardless of whether or not the participant has discontinued treatment/taken a prohibited medication.
		Population-level summary variable: Percent reduction of the placebo group change from baseline across Weeks 48, 72, and 96.
Secondary Efficacy	To evaluate the efficacy of AL001 compared with placebo in symptomatic participants as measured by CGI-I	**Target population:** Symptomatic carriers of a *GRN* mutation causative of FTD as defined by the inclusion and exclusion criteria.
		Variable of interest: Actual values at Weeks 48, 72, and 96 on the CGI-I.
		Intercurrent events and corresponding strategy: Study treatment discontinuation/prohibited concomitant medications (Treatment Policy). All observed values of the variable of interest, regardless of whether or not the participant has discontinued treatment/taken a prohibited medication.
		Population-level summary variable: Percent reduction of the placebo group values across Weeks 48, 72, and 96.
Secondary Efficacy	To evaluate the efficacy of AL001 compared with placebo in symptomatic participants as measured by the FRS	**Target population:** Symptomatic carriers of a *GRN* mutation causative of FTD as defined by the inclusion and exclusion criteria.
		Variable of interest: Change from baseline to Week 48, 72 and 96 in the FRS.
		Intercurrent events and corresponding strategy: Study treatment discontinuation/prohibited concomitant medications (Treatment Policy). All observed values of the variable of interest, regardless of whether or not the participant has discontinued treatment/taken a prohibited medication.
		Population-level summary variable: Percent reduction of the placebo group values across Weeks 48, 72, and 96.

Table 1: Study Objectives and Endpoints (Continued)

Part 1 Double-Blind, Placebo-Controlled Treatment Period: Study Objectives and Endpoints		
Secondary Efficacy	To evaluate the efficacy of AL001 compared with placebo in symptomatic participants as measured by RBANS	**Target population:** Symptomatic carriers of a *GRN* mutation causative of FTD as defined by the inclusion and exclusion criteria.
		Variable of interest: Change from baseline to Weeks 48, 72, and 96 on the RBANS.
		Intercurrent events and corresponding strategy: Study treatment discontinuation/prohibited concomitant medications (Treatment Policy). All observed values of the variable of interest, regardless of whether or not the participant has discontinued treatment/taken a prohibited medication.
		Population-level summary variable: Percent reduction of the placebo group change from baseline across Weeks 48, 72, and 96.
Pharmacodynamic and Disease Biomarkers	To evaluate the treatment effect of AL001 compared with placebo as measured by pharmacodynamic and disease pathology biomarkers in the symptomatic population, the at-risk population, and all FTD participants (both symptomatic and at-risk).	• PGRN concentrations in optional CSF • NfL concentrations in serum and optional CSF • Structural volumetric MRI whole and regional brain volume
Safety	To evaluate the safety and tolerability of AL001 compared with placebo as measured by safety assessments and ADAs in the symptomatic population, the at-risk population, and all FTD participants (both symptomatic and at-risk).	• Incidence, nature, and severity of adverse events (AEs) and serious adverse events (SAEs) • Physical examination abnormalities • Neurological examination abnormalities • Changes in vital signs from baseline over time • Changes in electrocardiograms from baseline over time • MRI abnormalities • Changes in clinical laboratory tests from baseline over time • Sheehan-STS • Incidence of ADAs to AL001

Table 1: Study Objectives and Endpoints (Continued)

Part 1 Double-Blind, Placebo-Controlled Treatment Period: Study Objectives and Endpoints		
Exploratory Endpoints	To evaluate the effects of AL001 compared with placebo as measured by:	
	Exploratory Quality of Life Objective: • Quality of Life COAs	*Exploratory Quality of Life Endpoints:* • EQ-5D score • ZBI score
	Exploratory Pharmacoeconomic Objective: • Pharmacoeconomic COA	*Exploratory Pharmacoeconomic Endpoint:* • RUD-Lite score
	Exploratory PD and Disease Biomarker Objective: • Exposure-response relationships • Exploratory imaging	*Exploratory PD and Disease Biomarker Endpoints:* • Exposure-response relationships for relevant biomarkers (eg, PGRN, NfL), efficacy, or safety responses in relation to AL001 exposure • Arterial spin labeling, diffusion-tensor imaging, and other MRI measures
	Exploratory COA Objective: • WLA	*Exploratory COA Endpoints:* • WLA, for participants who agree to participate in these optional assessments only
Part 2 Optional Open-Label Extension: Study Objectives and Endpoints		
	Objectives	**Endpoint**
Primary	To assess the long-term safety and tolerability of AL001 in participants who have completed Part 1 of the study	• Incidence, nature, and severity of AEs and SAEs • Physical examination abnormalities • Neurological examination abnormalities • Changes in vital signs from baseline over time • Changes in electrocardiograms from baseline over time • MRI abnormalities • Changes in clinical laboratory tests from baseline over time • Sheehan-STS • Incidence of ADAs to AL001

Table 1: Study Objectives and Endpoints (Continued)

Part 2 Optional Open-Label Extension: Study Objectives and Endpoints		
Exploratory Endpoints	COAs, correlative assessments (eg, 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 Part 1 of the study on the following:	
	• Treatment effect of AL001 compared with placebo as measured by disease pathology biomarkers	• PGRN concentrations in plasma • NfL concentrations in serum • Structural volumetric MRI whole and regional brain volume; arterial spin labeling, diffusion-tensor imaging, and other MRI measures
	• Clinical progression as measured by COAs	The overall change from baseline on the scores of the instruments in the COAs • CDR® plus NACC FTLD • CGI-I • CGI-S • RBANS • FRS • WLA, for participants who agree to participate in these optional assessments only
	• Quality of Life COAs	• EQ-5D score • ZBI score
	• Pharmacoeconomic COA	• RUD-Lite score
	• Exposure-response relationships	• Exposure-response relationships for relevant biomarkers (eg, PGRN, NfL), efficacy, or safety responses in relation to AL001 exposure

ADA=antidrug antibody; CDR® plus NACC FTLD-SB=Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center frontotemporal lobar degeneration Behavior and Language Domains Sum of Boxes; CGI-I=Clinical Global Impression-Improvement; CGI-S=Clinical Global Impression-Severity; COA=clinical outcome assessment; CSF=cerebrospinal fluid; EQ-5D=European Quality of Life-5 Dimensions; FTD=frontotemporal dementia; FRS=Frontotemporal Dementia Rating Scale; *GRN*=progranulin gene; MRI=magnetic resonance imaging; NfL=neurofilament light chain; PD=pharmacodynamic; PGRN=progranulin protein; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; RUD-Lite=Resource Utilization in Dementia-Lite version; Sheehan-STS=Sheehan-Suicidality Tracking Scale; WLA=Winterlight Labs Speech Assessments; ZBI=Zarit Burden Interview.

3. INVESTIGATIONAL PLAN

3.1. Study Design

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

Part 1 is a 96-week, randomized, double-blind, placebo-controlled treatment period to evaluate the efficacy and safety of AL001 60 mg/kg, q4w compared to placebo in participants who are carriers of heterozygous loss-of-function *GRN* mutations causative of FTD.

Part 2 is an optional 96-week OLE period for eligible participants who have completed Part 1. Part 2 will evaluate the long-term safety and tolerability of open-label AL001 60 mg/kg, q4w.

Each participant must be a known carrier of a heterozygous loss-of-function *GRN* mutation causative of FTD with a global Clinical Dementia Rating Scale (CDR®) plus NACC FTLD score of 0 to 2, and:

- Participants with a CDR® plus NACC FTLD-SB score ≤0.5 must have an elevated serum NfL (at-risk participants), or
- Participants with a CDR® plus NACC FTLD-SB score >0.5 must have 1 or more of the 6 behavioral/cognitive symptoms required for a diagnosis of possible bvFTD (Rascovsky 2011), or a diagnosis of PPA (Gorno-Tempini 2011) (symptomatic participants).

Part 1 (Double-Blind, Placebo-Controlled Treatment Period):

- Part 1 of the study is a 96-week randomized, double-blind, placebo-controlled treatment period to evaluate the efficacy and safety of AL001 compared to placebo in participants who are carriers of heterozygous loss-of-function *GRN* mutations causative of FTD.

Eligible participants will be randomly assigned, in a double-blind fashion, to receive AL001 (60 mg/kg) or placebo in a 3:2 ratio (AL001:placebo) q4w IV for 96 weeks. Participants will be stratified by:

- CDR® plus NACC FTLD-SB score ≤0.5
- CDR® plus NACC FTLD global score 0.5 (with a CDR® plus NACC FTLD-SB >0.5)
- CDR® plus NACC FTLD global score 1
- CDR® plus NACC FTLD global score 2

Part 2 (Optional Open-Label Extension):

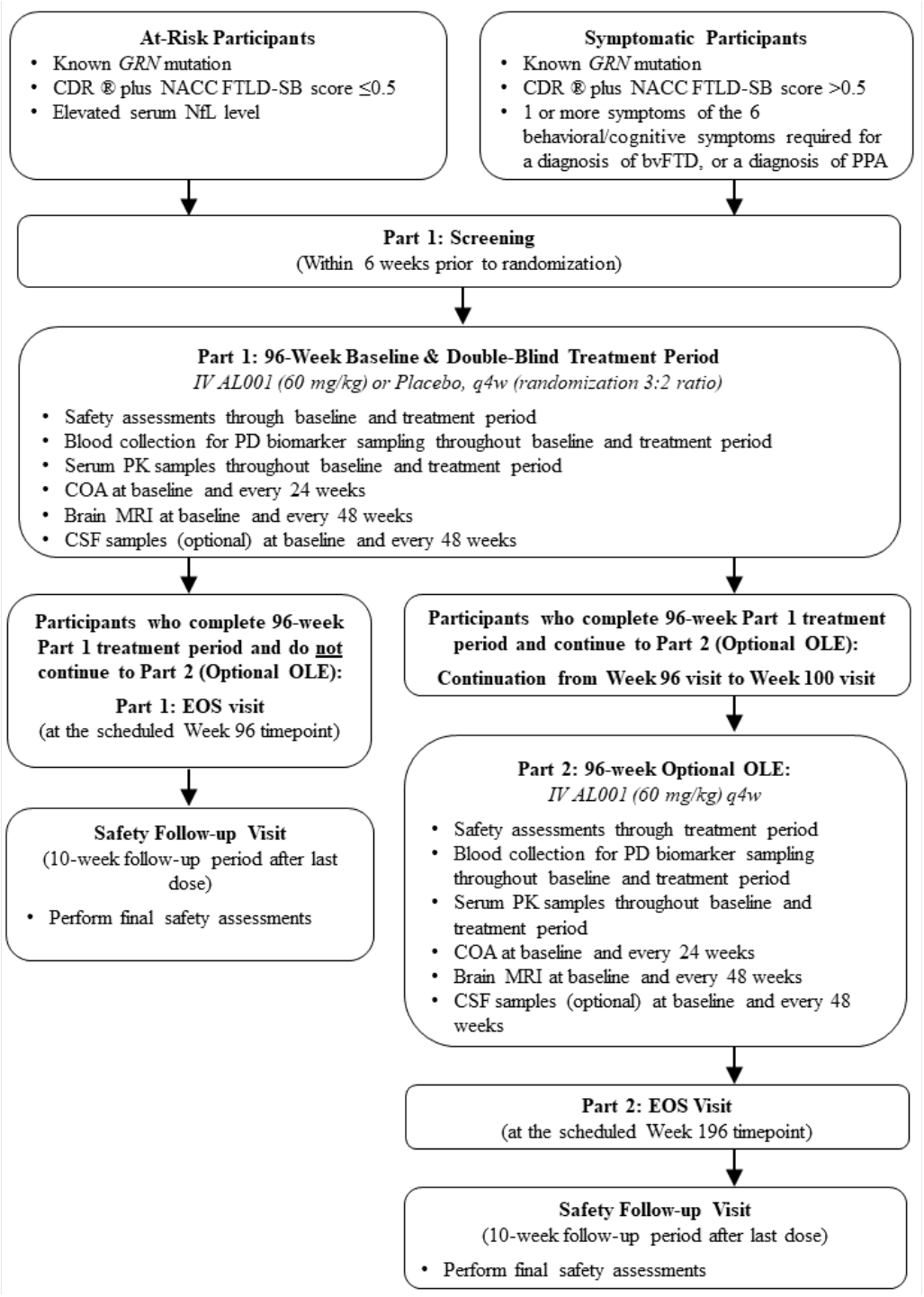
Part 2 of the study is an optional, 96-week, OLE to assess the long-term safety and tolerability of AL001 in participants who have completed Part 1 of the study. Continuation in the OLE is optional for Part 1 participants. A Part 1 participant may be excluded from continuing in the Part 2 OLE if, in the opinion of the Investigator, continued treatment with AL001 at the conclusion of Part 1 is not beneficial or safe for the participant. Part 1 participants who have

been admitted to a nursing home/assisted living facility are not eligible for participation in the OLE.

Treatment assignment in Part 1 (AL001 or placebo) will remain blinded to investigators and participants until Part 2 has been completed and the Part 2 data for all participants have been cleaned and locked. In addition, the Sponsor will remain blinded to treatment assignment in Part 1 until Part 1 has been completed and the Part 1 data for all participants have been cleaned and locked. All participants in the OLE, whether they received AL001 or placebo in Part 1, will receive open-label AL001 at a dose of 60 mg/kg, q4w.

An individual participant may continue to receive AL001 (60 mg/kg) in the OLE portion of the study for up to 25 doses over a 96-week dosing period for a total exposure of up to 196 weeks.

Figure 1: Study Design



bvFTD=behavioral variant frontotemporal dementia; CDR® plus NACC FTLD=Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center frontotemporal lobar degeneration Behavior and Language Domains; COA=clinical outcome assessment; CSF=cerebrospinal fluid; *GRN*=progranulin gene; IV=intravenous(ly); MRI=magnetic resonance imaging; NfL=neurofilament light chain; PD=pharmacodynamic; PK=pharmacokinetic; PPA=primary progressive aphasia; q4w=every 4 weeks.

3.2. Study Duration

Part 1 (Double-Blind, Placebo-Controlled Treatment Period):

- A screening period (within 6 weeks prior to randomization)
- A treatment period (96 weeks, Day 0 [first dose of study treatment] through Week 96)
- A 10-week Safety Follow-up period concluding with the Study Completion Visit
- Participants who discontinue study treatment prior to completing the 96-week Part 1 treatment period should be encouraged to complete all remaining scheduled assessment visits through Part 1 (including Clinical outcome assessments [COAs], magnetic resonance imaging [MRI], and CSF evaluations)
  - A Part 1 End of Treatment (EOT) visit will be completed by participants who discontinue study treatment 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 Safety Follow-up visit will be performed 10 weeks after their last study treatment administration.
  - A Part 1 End of Study (EOS) visit will be completed by participants who discontinue study treatment and all assessments before Week 97. Part 1 EOS assessments should be completed as soon as possible after the decision is made. A Safety Follow-up visit will be performed 10 weeks after their last study treatment administration.
- Participants who complete the Part 1 96-week treatment period will have the option to continue to receive AL001 in Part 2 (OLE) of the study
  - Participants who do not continue in Part 2 will complete a Part 1 EOS visit at the scheduled Week 96 visit. A Safety Follow-up visit will be performed 10 weeks after their last study treatment administration.
  - Participants who continue in Part 2 will complete the Week 96 visit and enter Part 2 at the Week 100 visit.

Part 2 (Open-Label Extension Period)

- A treatment period with open-label AL001 (96 weeks, Week 100 through Week 196), or until AL001 is commercially available in the country where the participant is being treated, whichever is earlier.
- Participants who discontinue AL001 and/or all assessments prior to completing 96 weeks of treatment will complete a Part 2 EOS visit as soon as possible after the decision to discontinue is made. A Safety Follow-up visit will be performed 10 weeks after the final AL001 administration.
- At Week 196, participants who complete 96 weeks of treatment with AL001 will complete a Part 2 EOS visit at the scheduled Week 196 time point. A Safety Follow-up visit will be performed 10 weeks after the final study treatment administration unless they will continue to receive AL001 under another Alector protocol or program.

3.3. Description of Study Periods

3.3.1. Part 1 - Double-blind, Placebo-controlled Treatment Period

Optional Pre-screening to Confirm Presence of Known Genetic Mutations Associated with Frontotemporal Dementia (including GRN Mutations)

All study participants must be known carriers of a heterozygous loss-of-function *GRN* mutation causative of FTD to be eligible to participate in the study (see Part 1 Eligibility Criterion #1). Participants may be pre-screened to determine the presence of a *GRN* mutation. If pre-screening is required, the participant must provide informed consent for the pre-screening assessment of the presence of *GRN* mutations and other known common genetic mutations associated with Frontotemporal Dementia, with genetic counseling highly recommended.

Optional Pre-screening to Confirm Presence of Elevated Serum NfL Levels

At-risk study participants (CDR® plus NACC FTLD-SB score ≤0.5) must have an elevated serum NfL level. Participants may be pre-screened to determine if their serum NfL level is elevated. If pre-screening is required, the participant must provide informed consent for the pre-screening assessment of the serum NfL levels. Elevated serum NfL levels obtained ≤90 days prior to study treatment administration can be used to satisfy eligibility.

Screening Period

To determine eligibility for entry into the study, participants must provide informed consent for the study and screening procedures may be performed within 6 weeks prior to randomization (Day -42 to Day 0).

Participants will undergo a screening evaluation with MRI, blood sampling for NfL biomarker measurement, routine safety laboratory, and other safety assessments. COAs, including those performed by the participant and their study partner, will be conducted at Screening. For participants who consent to optional lumbar punctures, CSF will also be collected at baseline prior to study treatment administration.

Randomization

Eligible participants will be randomly assigned to receive AL001 or placebo. Randomization will occur prior to or on Day 0. Study treatment administration on Day 0 will not be administered until all baseline assessments are completed and the participant has met all eligibility criteria.

Double-Blind Treatment Period

The planned study treatment period will be 96 weeks. Study treatment (AL001 60 mg/kg or placebo) will be administered IV q4w for a total of 25 doses. Clinical outcome assessments, including those performed by the participant and their study partner (study partner is described in Section 4.1.1), will be conducted every 24 weeks. Imaging will be performed every 48 weeks. Optional lumbar puncture for CSF collection will be performed every 48 weeks. Accepted windows for treatment, clinical assessments, and imaging are provided in the Schedules of Assessments (Table 3, Table 4, and Table 5).

Every effort will be made to follow all randomized participants for the full Part 1 96-week study treatment period, regardless of whether they discontinue study treatment. All participants will be followed for safety at 10 weeks after the last dose of study treatment.

Upon completion of the double-blind study treatment period (Week 96), participants who are eligible and provide consent will continue in Part 2 (Optional OLE) of the study. Part 1 participants who do not continue in Part 2 (Optional OLE) of the study will return to the investigational site 10 weeks after their last dose of study treatment for final safety assessments.

3.3.2. Part 2 - Optional OLE

Eligibility Confirmation

There is no screening period for participants who elect to enroll in Part 2 (OLE) of the study. Participants who, after completing Part 1, provide informed consent to participate in Part 2 and meet all the eligibility criteria for the OLE (determined prior to Week 100), may receive open-label AL001 according to the OLE administration schedule.

Treatment Period

The Part 2 OLE period will be up to 96 weeks. Open-label AL001 60 mg/kg will be administered IV q4w for a total of up to 25 doses. Blood sampling for safety, clinical outcome assessments, including those performed by the participant and their study partner, and imaging will be performed. Accepted windows for treatment, clinical assessments, and imaging are provided in the Schedules of Assessments (Table 6, Table 7, and Table 8).

OLE participants who discontinue study treatment early (eg, due to participant decision, withdrawal criteria, or AL001 commercial availability in the country where the participant in being treated) will be followed for safety at 10 weeks after the last dose of AL001.

4. PARTICIPANT SELECTION AND WITHDRAWAL CRITERIA

4.1. Selection of Part 1 Study Population (Double-blind, Placebo-controlled Treatment Period)

Participants at risk for or with FTD due to a heterozygous loss-of-function mutation in the *GRN* gene are planned to be enrolled at approximately 60 investigational sites globally.

Participants will be randomly assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

4.1.1. Inclusion Criteria - Part 1

Each prospective participant must meet all of the following criteria to be enrolled in this study:

Inclusion Criteria:

1. Is a known carrier of a heterozygous loss-of-function *GRN* mutation causative of FTD with a global CDR® plus NACC FTLD score of 0 to 2, and:
   - A CDR® plus NACC FTLD-SB score ≤0.5 with an elevated level of serum NfL, or
   - A CDR® plus NACC FTLD-SB score of >0.5 with 1 or more of the 6 behavioral/cognitive symptoms required for a diagnosis of possible bvFTD (Rascovsky 2011), or a diagnosis of PPA (Gorno-Tempini 2011).
2. Age 25 to 85 years, inclusive, at Screening.
3. At Screening, women must be nonpregnant and nonlactating, and 1 of the following conditions must apply:
   a. Not a woman of childbearing potential (WOCBP) (either surgically sterilized or physiologically incapable of becoming pregnant, or at least 1-year post-menopausal [amenorrhea duration of 12 consecutive months with no identified cause other than menopause]).
   b. Is a WOCBP and agrees to use an acceptable contraceptive method from Screening until 10 weeks after the last dose of study treatment. Acceptable contraception is defined as using hormonal contraceptives (eg, combined oral contraceptive pill) or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm, cervical cap, or condom. In addition, total abstinence, if in accordance with the lifestyle of the participant, is acceptable.
   c. WOCBP must have a serum pregnancy test conducted at screening. Additional requirements for pregnancy testing during and after study intervention are described in the Schedules of Assessments.
4. Men must agree to use acceptable contraception and not donate sperm from Day 0 until 10 weeks after the last dose of study treatment. Acceptable contraception for the male participant when having sexual intercourse with a WOCBP who is not currently pregnant is defined as using a condom. In addition, WOCBP partners must use hormonal contraceptives (eg, combined oral contraceptive pill) or an intrauterine device.
5. Agrees not to donate blood or blood products for transfusion for the duration of the study and for 1 year after the final dose of study treatment.

6. Willing to and can comply with the study protocol requirements, in the opinion of the Investigator.
7. Willing and able to give informed consent. If the patient is not competent, a legally authorized representative must provide informed consent on their behalf, and the patient must provide assent, in accordance with local regulations, guidelines, and institutional review board (IRB) or independent ethics committee (IEC).
8. Patient has the availability of a person ("study partner") who has frequent and sufficient contact with the patient (at least 5 hours per week of in-person contact) and who can provide accurate information to the study site regarding the patient's behavior, cognitive, and functional abilities, as well as their health, throughout the study. Requirements for the study partner include:
    a. Willing and able to provide informed consent to participate in the study as a study partner.
    b. The study partner must have sufficient cognitive capacity to accurately report upon the participant's behavior, cognitive, and functional abilities, in the opinion of the Investigator.
    c. The study partner should be in sufficiently good general health to have a high likelihood of maintaining the same level of interaction with the participant and participation in study procedures throughout the study duration.
    d. The same study partner should participate throughout the duration of the study. If a change in study partner is necessary, the Medical Monitor must be contacted.
    e. Study partner agrees to provide information at investigational site visits that require partner input for COA completion.
    f. Study partner agrees to accompany the participant at COA visits, as follows:
        - **At-risk participants** (CDR® plus NACC FTLD-SB score ≤0.5) require the study partner at the COA visits only.
        - **Symptomatic participants** (CDR® plus NACC FTLD-SB score >0.5) require the study partner at each visit.
        - **At-risk participants who become symptomatic** (CDR® plus NACC FTLD-SB >0.5) during the study treatment period require the study partner at each visit moving forward through Study Completion.

Inclusion criteria applicable to those participants participating in the optional Winterlight Labs Speech Assessment (WLA) only:

1. Has available and willing study partner to administer the WLA.
2. Has WiFi access in their residence or WiFi access in a private area where the testing can take place.
3. Participants and study partners must be proficient in English, Spanish, French, Dutch, or German in the Investigator's opinion.

4.1.2. Exclusion Criteria - Part 1

Prospective participants meeting any of the following criteria will be excluded from the study:

1. Dementia due to a condition other than FTD including, but not limited to, Alzheimer's disease, Parkinson's disease, dementia with Parkinsonism, rapid eye movement (REM) behavior disorder, dementia with Lewy bodies, Huntington disease, or vascular dementia.
2. Known mutation causative of neurodegenerative disorder(s) other than heterozygous loss-of-function *GRN* mutations causative of FTD.
3. Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins.
4. Signs or symptoms of progressive supranuclear palsy or bulbar dysfunction, such as postural instability, eye problems, and swallowing difficulties.
5. History of moderate or severe substance use disorder within the past 2 years, with the exception of nicotine, as defined by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition criteria (American Psychiatric Association 2013).
6. Clinically significant vitamin B12 or folate deficiency (if treated, must be on a stable regimen for at least 3 months prior to first study treatment administration).
7. Untreated hypothyroidism (if treated, thyroid supplementation dose must be stable for at least 3 months with a normal thyroid-stimulating hormone level prior to study treatment administration).
8. Insufficiently controlled diabetes mellitus (eg, hemoglobin A1C ≥8%).
9. Any surgery (major or emergent) or hospitalization within 30 days prior to first study treatment administration.
10. Participant has a history of cancer except if it:
    a. Is considered likely to be cured or in remission for at least 12 months,
    b. Is not being actively treated with anticancer therapy or radiation and, in the opinion of the Investigator, is not likely to require treatment in the ensuing 3 years,
    c. Is considered to have low probability of recurrence (with supporting documentation from the treating oncologist if possible), including participants with ongoing antihormonal treatment (eg, tamoxifen),
    d. For prostate cancer, has not had significant progression within the past 2 years, and is stable and adequately controlled,
    e. For localized skin basal cell carcinoma or squamous cell carcinoma, the participants should continue with screening and seek treatment for the skin carcinoma.
11. Positive for hepatitis B surface antigen, human immunodeficiency virus 1 or 2 antibodies or antigen, or history of spirochetal infection of the CNS (eg, syphilis, borreliosis, or Lyme disease). Participants with a positive or equivocal hepatitis C virus antibody will be allowed to enroll if hepatitis C RNA is confirmed negative.

12. Significant kidney disease as indicated by either of the following:
    a. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, according to the re-expressed abbreviated (4-variable) Modification of Diet in Renal Disease (MDRD) Study equation,
    Note: MDRD equation is as follows:

    eGFR (mL/min/1.73 m^2) = 175 × (standardized serum creatinine) $^{-1.154}$ × (Age) $^{-0.203}$ × (0.742 if female) × (1.212 if Black), or

    b. Creatinine ≥2 mg/dL.
13. Impaired hepatic function as indicated by screening aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5 × the upper limit of normal (ULN), and total bilirubin ≥1.5 × ULN. Note: Participants with Gilbert's syndrome are eligible to participate if approved by the Medical Monitor.
14. Clinically significant hematologic abnormalities as indicated by hemoglobin ≤10 g/dL; white blood cells (WBC) ≤3,000/mm^3; absolute neutrophil count ≤1,000/mm^3; or platelet count ≤150,000/mm^3.
15. Participants with hypertension who are not adequately and stably controlled as per the American College of Cardiology/American Heart Association (ACC/AHA) guidelines.
16. History or presence of an abnormal ECG that is clinically significant, including complete left bundle branch block, second- or third-degree atrioventricular block, or evidence of acute or subacute myocardial infarction or ischemia.
17. History of or concurrent clinically significant cardiovascular disease such as but not limited to myocardial infarction, angina pectoris, New York Heart Association Class III or IV cardiac failure, ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (eg, severe left ventricular systolic dysfunction, left ventricular hypertrophy). If the condition is stable per the consulting cardiologist, then the patient can enroll at the Investigator's discretion.
18. Clinically significant electrolyte abnormalities (eg, hypokalemia, hypomagnesemia, hypocalcemia).
19. For participants who consent to lumbar puncture, participant has contraindication to lumbar dural puncture, including coagulopathy, concomitant anticoagulation medication (except for a platelet inhibitor such as aspirin), thrombocytopenia, or other factor(s) that precludes safe lumbar puncture.
20. History or presence of clinically evident vascular disease potentially affecting the brain (eg, clinically significant carotid or vertebral artery stenosis or plaque; cerebral hemorrhage or infarct greater than 1 cm^3; 3 or more lacunar infarcts in any location; cerebral contusion; encephalomalacia; intracranial aneurysm; arteriovenous malformation; subdural hematoma); hydrocephalus; space occupying lesions (eg, abscess or brain tumor such as meningioma) that have the potential to affect cognitive function; or intracranial tumor that is clinically relevant (eg, glioma, cerebral metastasis).
21. History of a clinically significant, persistent neurologic deficit, structural brain damage, or CNS trauma.

22. Resides in a skilled nursing facility, convalescent home, or long-term care facility at screening; or requires continuous nursing care (ie, >3 months).
23. Unable to tolerate the required safety portion (as defined in the imaging manual) of MRI procedures (eg, due to anxiety or claustrophobia) or has a contraindication to MRI, including, but not limited to, the presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that are not compatible with an MRI scan; or any other clinical history or examination finding that would pose a potential hazard in combination with MRI. Use of conscious sedation is allowed to aid with tolerance of imaging procedures.
24. Has a medical condition or extenuating circumstance that, in the opinion of the Investigator, might compromise the participant's ability to comply with the protocol-required testing or procedures, or compromise the participant's well-being, safety, or clinical interpretability.

4.2. Selection of Part 2 Study Population (Optional OLE)

4.2.1. Inclusion Criteria - Part 2

The OLE is optional for participants who complete Part 1 of the study. Participants who complete Part 1 (96 weeks) of the study are eligible for continued treatment with AL001, provided that all of the following criteria are met:

1. Participant is willing and able to give informed consent to continue treatment with AL001. If the study participant is not competent, a legally authorized representative must provide informed consent on his or her behalf and the participant must provide assent, in accordance with the local regulations, guidelines, and IRB or IEC.
2. Is willing and has the ability to comply with OLE requirements, in the opinion of the Investigator.
3. Has availability of a person ("study partner") who can continue to assist with assessments throughout the OLE evaluation period. The study partner must have frequent and sufficient contact with the participant (at least 5 hours per week of in-person contact), have the ability to provide accurate information regarding the participant's cognitive and functional abilities as well as their health throughout the study. Requirements for the study partner include:
    a. Willing and able to provide informed consent to participate in the study as a study partner.
    b. The study partner must have sufficient cognitive capacity to accurately report upon the participant's behavior, cognitive, and functional abilities, in the opinion of the Investigator.
    c. The study partner should be in sufficiently good general health to have a high likelihood of maintaining the same level of interaction with the participant and participation in study procedures throughout the study duration.
    d. The Part 2 study partner can be the same individual as in Part 1, or can be a different individual, but the same Part 2 study partner should participate throughout the

duration of Part 2. If a change in study partner during Part 2 is necessary, the Medical Monitor must be contacted.

e. Study partner agrees to provide information at investigational site visits that require partner input for COA completion.
f. Study partner agrees to accompany the participant at COA visits, as follows:
   - **At-risk participants** (CDR® plus NACC FTLD-SB score ≤0.5) require the study partner at the COA visits only.
   - **Symptomatic participants** (CDR® plus NACC FTLD-SB score >0.5) require the study partner at each visit.
   - **At-risk participants who become symptomatic** (CDR® plus NACC FTLD-SB >0.5) during the study treatment period require the study partner at each visit moving forward through Study Completion.

4.2.2. Exclusion Criteria - Part 2

Part 1 participants are not eligible for continued treatment with AL001 in the OLE if any of the following apply:

1. Part 1 participant has been admitted to a skilled nursing facility, convalescent home, or long-term care facility at screening and requires continuous nursing care (ie, >3 months).
2. Part 1 participant has a medical condition or extenuating circumstance such that, in the opinion of the Investigator, continued treatment with AL001 at the conclusion of Part 1 is not beneficial or safe for the participant.

4.3. Prohibited and Restricted Medication Criteria - Part 1 and Part 2

The following medications are prohibited for a prespecified duration prior to Part 1 study start, as indicated, and during the entire period of study participation (Part 1 and Part 2). Participants who start these medications during the study at any time may be withdrawn from study treatment.

1. Any psychoactive cannabinoids at least 90 days prior to first study treatment administration on Part 1, unless approved by the Medical Monitor. Note: Cannabinoid use during the study is not permitted within 8 hours prior to any COA. Topical cannabinoid oil without tetrahydrocannabinol is allowable at any time.
2. Intermittent use of benzodiazepines or other sedatives (including second-generation antipsychotics used for sedation or anti-anxiolysis) during the 30 days prior to administration of first study drug. Chronic, stable use of these medications established for at least 90 days before administration of first dose is acceptable. If chronic, stable use begins after Day 1 of Part 1, it is at the Investigator's discretion if withholding is likely to adversely impact cognitive procedures. Premedication prior to lumbar puncture or MRI procedures is permitted during the study; however, use of benzodiazepines or other sedatives is not permitted within 2 days or 5 half-lives (whichever is longer) prior to any COA.
3. Any stimulant medication (eg, amphetamine, dextroamphetamine, dexmethylphenidate, lisdexamfetamine, methylphenidate) is prohibited unless prescribed as a stable regimen

for at least 90 days prior to the first study treatment administration on Part 1. Stimulant medications should not be initiated during the study.

4. Any sedatives, with the exception of sedatives used during the imaging procedure, are prohibited unless prescribed as a stable regimen for at least 90 days prior to the first study treatment administration and the dose should be kept as stable as possible during the study. All changes should be captured in the electronic case report form (eCRF). Antidepressants are allowed when prescribed as a stable regimen for at least 90 days prior to the first study treatment administration, or if started after randomization and maintained at a stable dose.
5. Any passive immunotherapy (immunoglobulin) or other long-acting biologic agent that is under evaluation to prevent or postpone cognitive decline within 1 year of Screening for Part 1.
6. Any exposure to an anti-sortilin antibody prior to enrollment in Part 1; use of any experimental oral therapy, biologic therapy, or any other investigational treatment within 90 days or 5 half-lives prior to the first study treatment administration on Part 1, whichever is longer.
7. Any experimental vaccine or gene therapy; routinely recommended vaccinations are allowed as well as any vaccine against SARS-CoV-2.
8. Typical (first-generation) antipsychotic or neuroleptic medication within 90 days prior to the first study treatment administration on Part 1, except as needed for brief treatment of a nonpsychiatric indication (eg, emesis).

   Use of atypical (second-generation) antipsychotic medications or use of pimavanserin is allowed during the study if treated with a stable regimen for at least 90 days prior to the first study treatment administration on Part 1. In addition, short-term use of these medications is permitted for treatment of anxiety and agitation, including study procedures. Short-term use should be stopped within 2 days or 5 half-lives (whichever is longer) prior to cognitive assessments.
9. Anticoagulation therapy is exclusionary for individuals who consent to lumbar puncture. *Note:* Use of aspirin or antiplatelet medication is allowed pre-study and during the study.
10. Systemic immunosuppressive therapy or use or anticipated systemic immunosuppressive therapy use during the study.
    a. Use of prednisone ≤10 mg/day or an equivalent corticosteroid is allowed during the study if treated with a stable regimen for at least 90 days prior to the first study treatment administration on Part 1, and participant has hemoglobin >9 g/dL, WBC count >3,000/mm^3, absolute neutrophil count >1,000/mm^3, and platelet count >100,000/mm^3.
    b. Treatment with steroids for acute exacerbations of asthma, chronic obstructive pulmonary disease (COPD), or flares of autoimmune conditions like Rheumatoid Arthritis is allowed for short-term use (eg, 10 days for asthma).

11. Chronic use of opioids (including long-acting opioid medication) within 30 days prior to the first study treatment administration on Part 1.
    a. Intermittent short-term use (<1 week) of opioid medications for pain is permitted pre-study and during the study, except within 2 days or 5 half-lives (whichever is longer) prior to any COA.

4.4. Withdrawal of Participants from Study Treatment and/or the Study

The duration of the study is defined for each participant as the date signed, written, informed consent is provided, through the End of Study Visit (Part 1 or Part 2)/Safety Follow-up Visit, whichever is later. The Study Completion section of the eCRF must be completed for all randomized participants.

In accordance with the Declaration of Helsinki and other applicable regulations, participants are free to withdraw from the study at any time and without penalty or loss of future medical care, or any other benefits to which they are otherwise entitled. The Investigator must discontinue any participant who requests to be withdrawn.

4.4.1. Criteria for Withdrawal from Study Treatment

For both parts of the study, a participant may be discontinued from study treatment at any time if the participant or the Investigator feels that it is not in the participant's best interest to continue.

The following is a list of possible reasons for study treatment discontinuation:

1. Participant is noncompliant with the protocol
2. Participant is lost to follow-up
3. Participant withdraws consent
4. Participant has a serious or intolerable AE that, in the opinion of the Investigator, requires withdrawal from the study treatment
5. Occurrence of an intercurrent illness that, in the opinion of the Investigator, will affect assessments of clinical status or safety to a significant degree
6. Use of a nonpermitted concomitant medication per Section 4.1.2
7. Pregnancy
8. Discretion of the Investigator
9. Participant has impaired hepatic function as indicated by ALT or AST ≥2.5 × ULN, and total bilirubin ≥2.0 × ULN. Note: Participants with Gilbert's syndrome are eligible to participate if approved by the Medical Monitor
10. Anaphylaxis
11. Infusion-related or injection-related reaction despite adequate premedication for an initial occurrence of a moderate to severe infusion-related reaction (Section 5.3.2) or if the participant experiences any of the following events: mucosal tissue involvement, airway compromise, or symptomatic hypotension with systolic blood pressure (BP) <90 mm Hg measured in the supine position.

If a participant is withdrawn from study treatment due to an AE or a SAE, the participant will be followed up by the Investigator until the abnormal parameter or symptom has resolved or stabilized (if applicable). The Investigator has the responsibility for all decisions regarding participant safety. It is recommended that the Investigator consult with the Medical Monitor prior to removing the participant from study treatment for any reason except participant withdrawal of consent and in case of medical emergency. Any participant may withdraw his or her consent at any time.

All participants who discontinue study treatment prior to the completion of the Part 1 96-week treatment period should be encouraged to complete all remaining scheduled assessment visits through the Part 1 treatment period (Week 96). Site personnel will follow-up to aid in this goal. The reason for the participant's early discontinuation of study treatment will be specified in the participant's source documents and in the eCRF.

A Part 1 EOT visit will be completed by participants who discontinue the study treatment 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 Safety Follow-up visit will be performed 10 weeks after the participant's last study treatment administration.

All Part 1 and Part 2 participants who discontinue the study treatment and all assessments prior to the scheduled Week 96 (Part 1)/Week 196 (Part 2) visit should be encouraged to return to the site for an EOS visit. EOS assessments should be completed as soon as possible after the decision is made. A Safety Follow-up visit will be performed 10 weeks after the participant's last study treatment administration.

Reasonable attempts will be made by the Investigator to obtain reasons for participant withdrawals (eg, 2 documented telephone calls on different days, followed by 1 registered letter). The reason for the participant's withdrawal from the study will be specified in the participant's source documents and in the eCRF.

4.4.2. Replacements

Participants who discontinue study treatment or withdraw from the study (Part 1 or Part 2) will not be replaced.

5. STUDY TREATMENTS

An interactive response technology (IRT) will be used to maintain a central log documenting screening, to implement randomization, to assess current inventories of AL001 and placebo, to initiate any necessary resupply of AL001 or placebo, and to document discontinuation of study treatment.

The IRT will assign carton and vial numbers and provide instructions for dispensing study treatment (AL001 or placebo).

5.1. Part 1 (Double-blind, Placebo-controlled Treatment Period)

5.1.1. Blinding

In Part 1 of the study, eligible participants will be randomly assigned to AL001 or placebo based on a randomization schedule prepared by the clinical research organization (CRO) before the start of the study. The IRT system will be used to administer the randomization schedule. Blinding procedures for the study are detailed in the Site Blinding Plan, Blind Maintenance Plan, and the Pharmacy Manual.

5.1.2. Breaking the Blind

Treatment assignment in Part 1 (AL001 or placebo) will remain blinded to investigators and participants until Part 2 has been completed and the Part 2 data for all participants have been cleaned and locked. In addition, the Sponsor will remain blinded to treatment assignment in Part 1 until Part 1 has been completed and the Part 1 data for all participants have been cleaned and locked. In the event that the blind needs to be broken because of a medical emergency, the Investigator may unblind an individual participant's treatment assignment through the IRT. The date on which the code was broken, together with the identity of the person responsible, must also be documented. Alector recommends, but does not require, that the Investigator contact the Medical Monitor before breaking the blind. Treatment assignment should not be disclosed to the Medical Monitor.

Maintaining blinded treatment is critical for the integrity of the clinical study, and therefore, if a participant's treatment assignment is disclosed to the Investigator, the participant will be discontinued from study treatment. The participant may be eligible for the OLE after approval by the Medical Monitor.

Pharmacovigilance personnel may independently unblind a participant for expedited reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) or other events requiring expedited regulatory reporting. In addition, in the event of SUSARs, which are subject to expedited reporting, the Sponsor/CRO pharmacovigilance will unblind the affected cases to fulfill reporting requirements. For such cases, unblinding will be performed according to documented procedures and the unblinded information will be kept to authorized pharmacovigilance personnel.

5.1.3. Method of Assigning Participants to Treatment Groups

Participants will be randomly assigned on or before Day 0 to receive AL001 60 mg/kg or placebo using a 3:2 allocation ratio through the IRT.

Randomization will be stratified by:

- CDR® plus NACC FTLD-SB score ≤0.5
- Global CDR® plus NACC FTLD score 0.5 (with a CDR® plus NACC FTLD-SB >0.5)
- Global CDR® plus NACC FTLD score 1
- Global CDR® plus NACC FTLD score 2

Randomization will occur after all inclusion criteria have been met and before the first study treatment administration on Day 0. It is anticipated that participants will usually begin study treatment immediately after randomization.

5.2. Part 2 (Optional OLE)

Upon completion of the double-blind study treatment period (Week 96), qualified participants may be offered the choice to participate in the Part 2 optional OLE with AL001. Participants who enroll in the OLE (and their investigators) will remain blinded to the study treatment (AL001 or placebo) they received in Part 1 of the study until Part 2 has been completed and the Part 2 data for all participants have been cleaned and locked.

5.3. Treatments Administered

Part 1 (Double-Blind, Placebo-Controlled Treatment Period)

All participants will receive IV AL001 (60 mg/kg) or placebo on Day 0 and then q4w for a total of 25 doses over a 96-week period, according to the Schedule of Assessments (Table 6 and Table 7). Study treatment administration on Day 0 will not occur until all baseline assessments are completed.

Part 2 (Optional OLE)

Participants in the optional OLE will continue to receive open-label AL001 60 mg/kg IV q4w, for up to 25 additional doses over a 96-week dosing period, or until commercial availability of AL001 in the country where the participant is being treated, whichever is earlier.

5.3.1. Administration Instructions

Dosing solution preparation instructions will be provided separately in a Pharmacy Manual.

AL001 or placebo will be administered IV over approximately 60 minutes at the investigational site by the Investigator or appropriately delegated and trained site personnel. Study treatment administration will be recorded in the source documentation and in the eCRF.

Participants should be monitored for at least 60 minutes after the end of the infusion (Section 5.3.2) and after completion of all activities scheduled for that visit day, and then discharged at the discretion of the Investigator or qualified designee.

5.3.2. Infusion-related and Injection-related Reactions

All participants in Part 1 and Part 2 of the study will be monitored for infusion-related reactions or injection-related reactions during the infusion/injection and immediately afterwards for at least 60 minutes. Injection-related reactions can be localized at the site of the injection or systemic and should be treated per institutional guidelines. If a participant experiences a mild infusion-related reaction, the infusion should be halted. Once the reaction has resolved, the infusion rate may be resumed at half the most recently used rate (eg, from 60 mL/hr [1.0 mL/min] to 30 mL/hr [0.5 mL/min]). The infusion should be stopped immediately for any participant who experiences a moderate to severe infusion-related reaction (eg, fever or chills), and the participant should receive aggressive symptomatic treatment. The infusion should not be restarted before all symptoms have disappeared, and then it may be restarted at half of the initial rate. The infusion should not be resumed if there is a second occurrence or if the participant experiences any of the following events: mucosal tissue involvement, airway compromise, or symptomatic hypotension with systolic BP <90 mm Hg measured in the supine position.

In addition, in the event of an infusion-related reaction, a sample of whole blood should be obtained for PK serum and ADA assessment of AL001 or placebo, and testing should be performed for c-reactive protein, tryptase, and interleukin 6 (IL-6). Further details regarding infusion-related reactions are provided in the AL001 IB.

5.4. Identity of Investigational Product

5.4.1. Formulation

AL001 is provided as a sterile solution formulated at a concentration of 50 mg AL001/mL in an aqueous formulation containing 20 mM L-histidine/histidine HCl, 7.5% (w/v) sucrose, and 0.02% (w/v) polysorbate-80 at pH 5.5.

The placebo shares the same formulation as the study drug but lacks the AL001 human recombinant anti-human sortilin IgG1 monoclonal antibody.

AL001 and placebo vials provided for this study will be manufactured under current Good Manufacturing Practice (cGMP) and will be suitable for human use.

5.4.2. Packaging and Labeling

The container closure system for both AL001 and placebo consists of a 20R Type I (EP-compliant) clear glass vial with a coated bromobutyl rubber stopper and a flip-off type aluminum crimp seal with blue cap.

Part 1: Each single-use vial will contain at least 20 mL of AL001 or 20 mL of placebo intended for IV use only.

Part 2: Each single-use vial will contain at least 20 mL of AL001 intended for IV use only.

AL001 and placebo will be manufactured for Alector under contractual and quality agreements at a qualified contract manufacturing organization and per cGMP. Alector will ensure that the products are labeled in accordance with all local regulatory requirements.

Blinding supplies are provided by Alector to mask potential color differences between AL001 and placebo dosing solutions. Further details regarding labeling, blinding supplies, and the unblinding of the investigational product are provided in the Pharmacy Manual.

5.5. Management of Clinical Supplies

5.5.1. Storage

The AL001 and placebo will be shipped and stored at a controlled temperature of 2°C to 8°C.

Upon receipt at the investigational site, the AL001 and placebo shall be stored securely under controlled and monitored conditions in a refrigerator set to maintain 2°C to 8°C. The AL001 and placebo vials should be protected from light and remain in the cartons provided until use. From preparation of dosing solution to administration at the investigational site, dosing solution storage time will be limited to 4 hours at ambient temperature and no more than 24 hours at 2°C to 8°C.

The investigators will be fully responsible for the security, accessibility, and storage of the AL001 and placebo while the vials are at their investigational facility.

5.5.2. Accountability

The investigational site will maintain accurate records of receipt of all AL001 and placebo, including dates and condition of receipt. In addition, accurate records will be kept regarding when and how much AL001 or placebo is dispensed and used by each participant in the study. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all AL001 and placebo will be reconciled and retained or destroyed according to applicable regulations.

5.5.3. Return or Disposal

Study product supplies, including partially used or empty vials, should be disposed of at the investigational site per local standard operating procedures (SOPs). If study product supplies cannot be destroyed on-site, they may be shipped back to the return depot. Please see the Pharmacy Manual for additional instructions.

5.6. Misuse for Illegal Uses

AL001 and placebo are supplied for use only in this clinical study and must not be used for any other purpose.

5.7. Prior and Concomitant Therapy

All concomitant medications used by a participant from informed consent through the Part 1/Part 2 EOS or Safety Follow-up visit, whichever is later, will be recorded in the participant's eCRF and coded using the World Health Organization Drug Dictionary (WHO-DD), Mar 2020 or later. 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.

During the course of the study, participants are anticipated to continue the use of acceptable prescribed medications identified during the screening procedures, in accordance with study inclusion and exclusion criteria. Participants should be advised against taking any new medication, both prescribed or over-the-counter, without consulting the Investigator, unless the new medication is required for emergency use.

Any concomitant medication deemed necessary for the welfare of the participant during the study may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded in full in the eCRF.

6. STUDY ASSESSMENTS AND PROCEDURES

Before undergoing any study procedures, all prospective participants and study partners will sign an informed consent form (ICF). If the prospective participant is not competent, a legally authorized representative must provide informed consent on their behalf and the prospective participant must provide assent, in accordance with the local regulations, guidelines, and IRB/IEC.

Participants and study partners will have the opportunity to have any questions answered before signing the ICF. The Investigator must address all questions raised by the participant and the study partner. The Investigator or designee will also sign the ICF. Further details of informed consent are provided in Section 10.3.

Timing and frequency of all assessments and procedures for Part 1 are presented in the Schedules of Assessments (Table 3 and Table 4) and the Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Sample Assessments (Table 5). Timing and frequency of all assessments and procedures for Part 2 are presented in the Schedules of Assessments (Table 6 and Table 7) and the Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Sample Assessments (Table 8). At-risk participants (CDR® plus NACC FTLD-SB score ≤0.5) require the study partner at the COA visits only; symptomatic participants (CDR® plus NACC FTLD-SB score >0.5) require the study partner at each visit. At-risk participants who become symptomatic (CDR® plus NACC FTLD-SB >0.5) during the study treatment period (Part 1 or Part 2) will require the study partner at each subsequent visit after being diagnosed as symptomatic.

Adaptations to visits and procedures due to inability to travel to the clinical site as scheduled are detailed in Section 6.4.

6.1. Timing of Study Treatment Administration

Pre-dose Procedures:

- Perform COAs prior to any potentially stressful procedure (eg, blood collections, lumbar punctures, imaging)
- Physical examination (PE) or symptom-directed examination
- Neurological examination or symptom-directed examination
- Vital signs (including BP, pulse, body temperature, and respiratory rate) and weight
- Triplicate 12-lead ECG
- Obtain blood and urine samples for chemistry, hematology, serology, pregnancy testing, urinalysis, and coagulation (if applicable)
- Obtain blood samples for ADAs, PK, and biomarkers
- Obtain blood sample for pharmacogenomic research (Part 1 only)
- Perform MRI
- Collect CSF samples via lumbar puncture (optional) for biomarkers and PK (Part 1 only)

- Perform Sheehan-STS
- Review of concomitant medication(s)
- Record any AEs and SAEs

Dosing Procedures:

- Study treatment will be administered to participants per institutional practice (Section 5.3).

Post-Dose Procedures:

- Obtain serum samples for PK
- Triplicate 12-lead ECG
- Vital signs (including BP, pulse, body temperature, and respiratory rate)
- Review of concomitant medication(s)
- Record any AEs and SAEs

6.2. Rescreening Criteria

Part 1 participants who are not enrolled within the Screening period will be considered screening failures. Rescreening may be allowed following approval of the Medical Monitor. Participants who are rescreened after the Screening period must be reconsented with a new Screening number and the Screening assessments must be repeated.

Prospective Part 1 participants who are rescreened may not be required to repeat the NfL, MRI imaging, or optional CSF assessment, if performed ≤90 days prior to study treatment administration, with approval from the Medical Monitor. COAs performed within 8 weeks prior to the first study treatment administration on Part 1 may not be required to be repeated, with approval from the Medical Monitor. Repeat pharmacogenomic sampling is not required, and there is no time restriction for repeating screening evaluations.

Note: It is not necessary to repeat the pre-screening tests for the presence of elevated serum NfL levels if these tests were previously performed ≤90 days prior to study treatment administration.

Rescreening is not applicable for Part 2 of the study.

6.3. Participant Enrollment and Treatment Assignment

Participant eligibility will be established at the conclusion of Part 1 screening evaluations. The Participant ID will be assigned for that individual participant by the designated IRT. It is the responsibility of the Investigator to ensure that each participant is eligible for the study before randomization. A participant will be considered enrolled once he or she has been randomized to study treatment. The participant will retain the same Participant ID throughout the study (ie, throughout Part 1 and Part 2).

6.4. Efficacy Assessments

The following COAs (described in Section 14.2) will be performed. All COAs will be performed prior to study treatment administration (if applicable) and prior to any stressful procedures (eg, blood collections, imaging, lumbar puncture).

- Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center frontotemporal lobar degeneration Behavior and Language Domains (CDR® plus NACC FTLD)
- Clinical Global Impression-Severity (CGI-S)
- Clinical Global Impression-Improvement (CGI-I)
- Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
- Frontotemporal Dementia Rating Scale (FRS)
- European Quality of Life-5 Dimensions (EQ-5D)
- Zarit Burden Interview (ZBI)
- Resource Utilization in Dementia-Lite Version (RUD-Lite)
- WLA (participants who agree and are eligible to participate in the optional assessments only)

A percentage of the CDR® plus NACC FTLD scales administered by investigational sites will be independently reviewed by a qualified third-party vendor for adherence to standardized administration and scoring guidelines to ensure accuracy of study endpoint data.

Specific information on the collection and data entry of COAs will be provided in a separate manual.

Restrictions on when to stop the use of medications known to impair consciousness or cognition prior to COAs are provided in Sections 4.1.1 and 4.1.2.

6.4.1. Remote Efficacy Assessments

If participants or study partners are not able to come to the hospital for a visit, the following assessments should be completed by telephone or video (if locally approved/allowed):

- Review of AEs and concomitant medications
- Review of medical history
- COAs per below can be completed remotely except for Baseline:

1. **Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center Frontotemporal Lobar Degeneration Behavior and Language Domains (CDR® plus NACC FTLD)**
   While it is strongly preferred that participants and caregivers receive administration of the CDR® plus NACC FTLD in person, it is understood that remote administration might be required due to extenuating circumstances. The CDR®NACC FTLD can be administered telephonically or by locally approved video conference capabilities.

   – **Recommendation:** Although the full CDR® plus NACC FTLD administration has not been validated for remote administration (ie, phone or video conferencing), remote administration by phone has been validated for 6 of the domains (Randolph 2014).

     Guidelines have been developed for telephone administration of the CDR and the CDR plus NACC FTLD have been developed by the National Alzheimer's Coordinating Center to allow data collection for participants who cannot attend an in-person assessment. The CDR plus NACC FTLD can be completed by an approved rater based on the information provided by the study partner/informant report. The assessment of the Behavior, Comportment, and Personality domain will be completed based on informant report and a review of information from the participant, as available. The Language domain can be completed based on informant report and if possible, the information from the participant that is based on a clinical assessment of their responses during the clinical interview and other supporting data where available.

   – Scoring anchors can be reliably differentiated for the remaining CDR® plus NACC FTLD 2 domains (language and behavior) via phone, however, video conferencing would yield more reliable data for scoring these domains. Furthermore, video conferencing eliminates the need to rely on the study partner for observations (eg, the rater can evaluate participant's appearance and facial expression or ask them to name objects in the room). Given the incremental differences between anchors, raters should be able to differentiate scores with adequate inquiry even if the rater, participant, and caregiver are not in the same room.

   – In the circumstance that the primary rater is remote, and the participant and backup rater are on-site, scales can still be administered by the primary rater. The primary rater should call in to the visit to administer the CDR® plus NACC FTLD questions over the video conference. The backup rater should observe the participant while they are answering the probes, and then provide observations of the participant's behavior to the primary rater. Missing data from direct observation, which cannot be provided by the primary rater, can be completed by the backup rater, as long as they are appropriately trained on the scale. The primary rater must make the final observational assessments.

2. **Clinical Global Impression (CGI)**

   - **Recommendation:** A general, unstructured evaluation, discussion with study partner, and a review of data collected from other scales (if not contraindicated by the protocol or study team instructions) may help ensure CGI raters have adequate information to score. The CGI is informed by the CDR® plus NACC FTLD interview.

3. **Frontotemporal Dementia Rating Scale (FRS), Resource Utilization in Dementia - Lite Version (RUD-Lite), Zarit Burden Interview (ZBI)**

   - **Recommendation:** As a clinician-administered interview with the study partner, the FRS, RUD-Lite, and ZBI can be administered in-person in the clinic, in home, telephonically, or via video conferencing.
     - In the circumstance that the primary rater is remote, and the participants and backup rater are on-site, scales can still be administered by the primary rater. The primary rater should call into the visit to administer the FRS, RUD-Lite, and ZBI questions over the phone.

4. **Sheehan-Suicidality Tracking Scale (S-STS)**

   - Recommendation**:** This can be completed via phone but in person is preferred. Per Dr. Sheehan's instructions, the rater must provide a copy of the scale to the participants to view when they are being evaluated (eg, via mail, email, screenshot). Prior to the assessment, confirm that the participant has received a copy of the scales.

Communication technologies to be used for remote COA administration are summarized in the following table:

Scale	Communication Technologies
CDR® plus NACC FTLD	Video Conference or Phone with the study partner/informant and participant (Please note that a phone assessment might be done with the participant depending on their level of impairment, however, the Language domain impairment should be taken into account and this should be approved by Alector prior to administration.)
CGI-I	Not Applicable; this is informed by the CDR® plus NACC FTLD interview
CGI-S	Not Applicable; this is informed by the CDR® plus NACC FTLD interview
FRS	Phone or Video Conference
RUD-Lite	Phone or Video Conference
Sheehan-STS	Phone or Video Conference
ZBI	Phone or Video Conference

The following general guidelines for administering scales telephonically or by video conference should be followed:

1. Always record on the notes page of the scale or in your source documents when a certain assessment was administered remotely and describe any accommodations made.
2. Ensure that scale administration guidelines indicated in the scale manual and tutorial are carefully followed when adapted for use via telephone or video conference.
3. Raters are encouraged to consider and address possible distractions which could affect performance during an assessment. This includes forms of distraction that may not be obvious or visible (eg, sight, sound, and smell). Consider the quality of the telecommunication technologies being used and the hardware requirements needed in order to conduct the specific assessment (eg, a telephone with speakerphone).
4. Always use the speaker phone for the scales that should be recorded for Independent Review.
5. Scales should be administered as if informant and/or participant were face-to-face with the rater and should be administered in a quiet, distraction-free interview environment.
6. There may be situations in which study partners or raters are remote. In these cases, the following guidance should be followed:
    a. If the study partner/caregiver is remote and the participant is on-site, scales can be administered per procedure, with study partner/caregiver providing answers to the site rater.
    b. If the primary rater is remote, and the participant and backup rater are on-site, scales can still be administered by the primary rater. The backup rater can be used to provide observational information to the primary rater, provided that they are trained on the scale. Refer to additional guidance under CDR® plus NACC FTLD and FRS sections.

6.4.2. Efficacy Assessments with Nonverbal Participants

For instances in which a participant has compromised language abilities, an attempt to collect data based on study partner/informant report and nonverbal cognitive tests should be made. Cognitive data are also important clinical markers of progression or a treatment effect since domains can be differentially affected throughout the disease course. As such, we provide the following recommendations for the assessments below:

Scale	Type of Response Needed	Instructions
CDR® plus NACC FTLD	study partner/informant reports at minimum	Please complete based on information obtained from the study partner/informant. Attempts to complete all aspects of the participant portion is encouraged and these data can be integrated to formulate clinical impressions to score the instrument.
CGI-I	study partner/informant reports	Please complete, this is informed by the CDR® plus NACC FTLD interview.
CGI-S	study partner/informant reports	Please complete, this is informed by the CDR® plus NACC FTLD interview.
FRS	study partner/informant reports	Please complete based on information obtained by the study partner/informant.

Scale	Type of Response Needed	Instructions
RUD-Lite	study partner/informant reports	Please complete based on information obtained by the study partner/informant.
Sheehan-STS	study partner/informant reports, nonverbal cognitive test, clinical observations	Please complete if participant is able. If participant is not able, please utilize site-specific procedures/PI discretion for evaluating suicidal ideation/behavior/attempts to ensure their safety.
ZBI	study partner/informant reports	Please complete based on information obtained by the study partner/informant.
RBANS	nonverbal cognitive test	Please attempt the following subtests with the participant: Figure Copy Line Orientation Picture Naming (with cues) Coding Figure Recall

6.5. Safety Assessments

Safety assessments include monitoring AEs; PEs; neurological examinations; vital signs and weight; ECGs; MRIs; clinical laboratory analyses in blood, urine; suicidality assessments; and ADAs.

6.5.1. Adverse Events

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 treatment that occur at any time should be reported by the Investigator regardless of the AE/SAE collection window. Definitions describing what is and is not considered an AE are provided in Section 7.

6.5.2. Concomitant Medications

All medication history and use of concomitant medications will be collected and recorded in the eCRF as described in Section 5.7.

6.5.3. Demographics

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

Alector is collaborating with the Genetic FTD Initiative (GENFI) study, a group of research centers across Europe and Canada with expertise in familial FTD, and the ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD) study, a study in the US and Canada targeting most varieties of frontotemporal lobar degeneration (FTLD). As part of the GENFI and ALLFTD studies, all clinical trial participants will have the option of having a National Institute on Aging (NIA) Global Unique Identifier (GUID) generated. The GUID is a secure, random alphanumeric identifier. It can be used to match participants across studies and datasets without disclosing participants' Personal Identifying Information or Personal Health

Information. The purpose of this GUID is to allow for the sharing of deidentified data and biospecimens between sponsors and GENFI and ALLFTD.

Participants in Study AL001-3 who are also participating in the GENFI or ALLFTD will have the option to have their NIA GUID collected by the investigational site personnel and recorded in the Study AL001-3 electronic data capture (EDC) system. Study AL001-3 participants who are not participating in GENFI or ALLFTD will have the option of the investigational site personnel assigning them a NIA GUID and recording it in the Study AL001-3 EDC system.

6.5.4. Medical History

All relevant medical history, including history of current disease, other pertinent history, and information regarding underlying diseases, will be recorded in the eCRF at screening prior to the first study treatment administration in Part 1.

A diagnostic characterization form will be completed in the eCRF for symptomatic participants at Screening, Week 96, and Week 196 (if applicable for symptomatic participants in the optional Part 2 OLE). It will also be completed for any at-risk participant who becomes symptomatic during the course of the study (CDR® NACC FTLD-SB score >0.5); for these participants, the diagnostic characterization form will be completed only at the first visit in which they exhibit clinical symptomatology and at all remaining scheduled study time points.

6.5.5. Physical Examinations

Complete PEs will include 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 the opinion of the health care provider. Symptom-directed PEs should include cardiovascular, respiratory, and gastrointestinal systems, plus any other pertinent system as required. The examination will be performed by a physician or by a nurse practitioner, or by a physician's assistant under the supervision of a physician.

Complete or symptom-directed examinations will be performed at time points indicated in the Schedule of Assessments (Section 14.1).

For visits with study treatment administration, PEs should be completed prior to the infusion. Additional examinations may be completed as clinically indicated.

Record abnormalities observed at screening on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the AE eCRF.

Height (cm) will be measured at Screening only.

6.5.6. Neurological Examinations

A complete neurologic examination should include the evaluation of consciousness, orientation, cranial nerves, motor and sensory system, coordination and gait, and reflexes. A symptom-directed examination should focus on the affected organ system or body area.

Complete or symptom-directed neurologic examinations will be performed at time points indicated in the Schedule of Assessments (Section 14.1). For visits with study treatment

administration, this should be completed prior to the infusion. Additional examinations may be completed as clinically indicated.

Record abnormalities observed at screening on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the AE eCRF.

6.5.7. Vital Signs and Weight

Systolic and diastolic BP, pulse, body temperature, and respiratory rate will be determined as per standard institutional practice.

Record abnormalities observed at screening on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities as AEs on the AE eCRF.

Weight (kg) will be collected (pre-dose only) at the same visits that vital signs are taken.

6.5.8. Electrocardiograms

Triplicate 12-lead ECGs will be obtained after the participant has been in the supine position for at least 5 minutes. Additional ECG monitoring must be performed during the treatment period, if clinically indicated.

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 in the eCRF. In addition, triplicate ECG tracings from Week 0 (pre-dose and post-dose), Week 24, and Week 48 for approximately 60-80 participants will be read by a core ECG laboratory (Note: Central ECG reads may not occur in real time; thus, these results will not be used for safety assessments during study conduct). Further details of central ECG review will be covered in a separate ECG manual.

6.5.9. Magnetic Resonance Imaging

MRI scans of the brain will be performed and reviewed by blinded independent radiologists at a central contract imaging vendor for assessment of safety, as well as for biomarker assessments (Section 6.6). Specific information regarding the collection and processing of MRI images will be provided in a separate manual.

Record abnormalities observed at screening on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities as AEs on the AE eCRF.

6.5.10. Laboratory Assessments

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 2.

For any laboratory test value outside the reference range that the Investigator considers clinically significant, the Investigator will follow the instructions in Section 7.1.

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

Table 2: Laboratory Assessments

<table>
<tr><th>Chemistry</th><th>Coagulation (optional)[a]</th><th>Hematology</th><th>Serology</th></tr>
<tr><td rowspan="3">Total bilirubin
Direct bilirubin
Alkaline phosphatase
Gamma GT
AST
ALT
LDH
Creatine kinase
Creatinine[b]
Urea
Uric acid
Cholesterol
HDL
LDL
Triglycerides
Total protein
Albumin
Glucose
Bicarbonate
Inorganic phosphate
Sodium
Potassium
Calcium
Chloride
Magnesium
Lipase</td><td>PT
INR
aPTT</td><td>HbA1c
Leukocytes
Erythrocytes
Hemoglobin
Hematocrit
Thrombocytes (platelets)
MCV
MCH
MCHC

Partial automated differentiation:
Lymphocytes
Monocytes
Eosinophils
Basophils
Neutrophils</td><td>anti-HCV
anti-HIV
HIV antigen
HBsAg
Total hepatitis B core antibody
HBsAb</td></tr>
<tr><td>Urinalysis</td><td colspan="2">Pregnancy Test</td></tr>
<tr><td>Hemoglobin (blood urine)
Ketones
Glucose
Protein
Leukocyte esterase
Nitrite
pH
Specific gravity
Microscopic analysis[d] (sediment, erythrocytes, leukocytes, casts, crystals, epithelial cells, and bacteria)</td><td colspan="2">Serum β-hCG or urine pregnancy test[c]</td></tr>
</table>

ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; β-hCG=β-human chorionic gonadotropin; GT=glutamyl transferase; HbA1c=hemoglobin A1c; HBsAb=antibody to hepatitis B surface antigen; 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 hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PT=prothrombin time.

[a] The coagulation panel will only be assessed for participants who have consented to optional cerebrospinal fluid sampling.

[b] Creatinine and calculation of estimated glomerular filtration rate (eGFR), as per the re expressed abbreviated (4 variable) Modification of Diet in Renal Disease (MDRD) Study equation. The MDRD equation is as follows: eGFR (mL/min/1.73 m^2) = 175 × (standardized serum creatinine) - 1.154 × (Age) - 0.203 × (0.742 if female) × (1.212 if Black).

[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 treatment 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.

6.5.11. Sheehan-Suicidality Tracking Scale

The Sheehan-STS (described in Section 14.2) is a brief scale designed to assess and monitor over time the core phenomena of suicidality. 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.

If the participant cannot complete the Sheehan-STS evaluation, a clinical evaluation of suicide risk should be completed by a medically qualified staff member. The completion and outcome of this assessment should be recorded in the eCRF and documented in the participant's source documents. Any indication of a risk of suicide should be immediately evaluated by the Investigator and reported to the Medical Monitor.

If the Investigator makes an evaluation and deems there to be suicidal ideation or behavior, an AE should be recorded.

6.5.12. Antidrug Antibodies

Blood serum samples will be collected for determination of ADAs.

Additional ADA samples should be collected in participants with signs and symptoms of infusion-related reactions (Section 7.7). 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 IL-6.

6.6. Pharmacodynamic and Disease Biomarker Assessments

PD and disease biomarker assessments will consist of blood-based biomarkers, CSF-based biomarkers (optional; when available), and imaging biomarkers, as follows:

Blood-based Biomarkers:

- Blood plasma samples will be collected for evaluation of PGRN
- Blood serum samples will be collected for evaluation of NfL levels.

CSF-based Biomarkers, Part 1 only (CSF collections apply to those participants who consent to the optional lumbar puncture only):

- CSF samples will be evaluated for levels of PGRN and NfL. See Section 6.10 for details of optional CSF sampling.

Imaging Biomarkers:

- MRI scans of the brain will be performed and centrally reviewed for:
  - Assessment of safety
  - Evaluation of global and regional brain volumes
  - Volume of white matter hyperintensities (measured by volumetric MRI)
  - Brain perfusion (measured by arterial spin labeling MRI)
  - Fractional anisotropy

- Mean diffusivity
- Axial diffusivity
- Radial diffusivity (measured by diffusion-tensor imaging)

Note: Specific information regarding the collection and processing of MRI images will be provided in a separate manual.

Other whole blood, plasma, and CSF biomarker samples will be collected for evaluation for neurodegeneration (eg, tau, phosphorylated tau), lysosomal function (eg, cathepsins), glial activity (eg, YKL40, IL-6), and messenger RNA expression and for potential evaluation of levels of other analytes relevant to disease biology, mechanism, and response to study treatment.

6.7. Pharmacokinetic Assessments

The PK assessments will consist of serum samples and optional CSF samples. Blood serum samples will be collected for assessment of serum concentrations of AL001. Cerebrospinal fluid samples will be assessed for concentration of AL001 (Part 1 only). See Section 6.10 for details of optional CSF sampling.

6.8. Pharmacogenomic Assessments

If allowed per local regulations, a blood sample will be collected for pharmacogenomic research with the goal of identifying common and rare genetic variants that are predictive of response to study treatment, 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.

This sample should be collected at the Part 1 Baseline visit but may be collected at any time during the study, if necessary.

Genomics is increasingly informing researchers' understanding of disease pathobiology. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of larger datasets will assist in identification of important pathways, guiding the development of new targeted agents.

6.9. Sample Collections

Specific information on clinical laboratory, ADAs, PK, PD and disease biomarker, and pharmacogenomic sample collection, processing, storage, and shipment will be provided in separate manuals.

Unused portions of PK and biomarker samples, and/or pharmacogenomic samples remaining after all applicable protocol-defined tests have been performed may be retained- and maintained, for up to 10 years, if the participant agrees and provides consent separately as described in Section 10.3. These samples may be used for future testing not described in this protocol. For participants who have provided consent, the samples may be used for testing including the following: further evaluation of biomarkers (eg, associated with efficacy, AEs, or disease progression), further clarification or characterization of the disease, further evaluation of AL001's effects, and/or development of assays (eg, biomarkers or diagnostic assays).

6.10. Optional Cerebrospinal Fluid Sampling

In Part 1, optional CSF samples will be collected via lumbar puncture prior to the first study treatment administration for symptomatic participants who provide consent at Screening, Week 48, Week 96, and/or the Part 1 EOS/EOT Visit to evaluate PK and biomarker measures. Any treated participant who has consented to the optional lumbar puncture assessment and discontinues prematurely should have CSF drawn, unless CSF has been drawn within 12 weeks of discontinuation.

Specific information on the collection, processing, storage, and shipment of CSF samples will be provided in a separate manual.

6.11. Unscheduled Visits

Unscheduled visits may occur at any time while the participant is enrolled in the study. Assessments should be performed as clinically indicated.

6.12. Part 1 End of Treatment Visit

Participants who discontinue study treatment prior to completing the 96-week Part 1 treatment period should be encouraged to complete all remaining scheduled assessment visits through Part 1 (including COAs, MRI, and CSF evaluations).

A Part 1 EOT visit will only be completed by participants who discontinue study treatment but remain in Part 1 of the study and continue to perform all assessments (Section 4.4.1). Part 1 EOT assessments should be completed as soon as possible after the decision is made.

The EOT visit may be substituted by a scheduled study visit if it occurs within the same window.

6.13. End of Study

The End of Study for a participant is defined as discontinuing study treatment and all assessments prior to completing the 96-week Part 1 treatment period, or prior to completing the 96-week Part 2 OLE period.

6.13.1. Part 1 End of Study Visit

Participants who discontinue study treatment and all assessments prior to completing the 96-week Part 1 treatment period (Section 4.4.1) will complete a Part 1 EOS visit as soon as possible after the decision to discontinue is made. The Part 1 EOS visit may be substituted by a scheduled study visit if it occurs within the same window.

Participants who complete the 96-week Part 1 treatment period, at Week 96, will have the option to continue to receive AL001 in Part 2 (OLE) of the study. Participants who do not continue in Part 2 will complete a Part 1 EOS visit at the scheduled Week 96 time point. Study treatment administration will only occur at the Part 1 EOS visit (at the scheduled Week 96 time point) for participants who complete the Part 1 96-week treatment period and who do not continue in Part 2.

Participants who continue in Part 2 will complete the Week 96 visit and continue to Part 2 (Week 100).

6.13.2. Part 2 End of Study Visit

Participants who discontinue open-label AL001 and/or all assessments prior to completing the 96-week Part 2 OLE period (Section 4.4.1) will complete a Part 2 EOS visit as soon as possible after the decision to discontinue is made. The Part 2 EOS visit may be substituted by a scheduled study visit if it occurs within the same window.

At Week 196, participants who complete the 96-week Part 2 OLE period will complete a Part 2 EOS visit at the scheduled Week 196 time point. Study treatment administration will only occur at the Part 2 EOS visit (at the scheduled Week 196 time point) for participants who complete the Part 2 96-week OLE period.

6.14. Safety Follow-up Visit

A Safety Follow-up visit will be performed 10 weeks following the last dose of AL001.

7. ASSESSMENT OF SAFETY

The Investigator is responsible for reporting all AEs and SAEs that are observed or reported during the study, regardless of their relationship to study treatment.

The Investigator's assessment of the relationship of an AE or SAE to study treatment is part of the documentation process, but it is not a factor in determining whether to record or report an AE/SAE in the study. If there is any doubt as to whether a clinical observation should be reported as an AE/SAE and the event is not a sign or symptom of another reported event, then observation should be reported as an AE/SAE.

Definition of Adverse Events

Adverse events are any untoward medical occurrence in a participant enrolled into this study, including side effects, injury, toxicity, sensitivity reaction, intercurrent illnesses, or sudden death, whether or not it is considered related to the study treatment. Participants will be instructed to contact the Investigator to report any AEs including if any symptoms develop at any time during study participation. All AEs must be appropriately documented in the participant's original source documents and on the eCRFs. When entering AEs and SAEs into CRFs, Investigators should report the diagnosis rather than list symptoms, whenever possible.

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

AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported within the established time frames. See (Section 7.2) for reporting requirements.

An AE does not include the following:

- Elective medical or surgical procedures planned prior to the start of study treatment (eg, hip replacement surgery) that did not result from a worsening of a previous condition (ie, prior to signing informed consent).

  Note: Any serious procedural complication or hospital-emergent conditions (eg, nosocomial infection) would be reported as an SAE.

- Any medical condition or clinically significant laboratory abnormality that has an onset date before the consent form is signed and that is not related to a protocol-associated procedure is not an AE. Such conditions are considered to be pre-existing and should be documented in the medical history eCRF. A pre-existing condition should be reported as an AE only if its frequency, intensity, or symptoms worsen during the course of the study.

- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for study treatment administration per institutional guidelines, elective surgery, social and/or convenience admissions).

Disease progression within expected parameters for the study population is not considered an AE. See (Section 7.2) for more information on reporting AEs associated with disease progression.

Serious Adverse Events

An SAE is defined as any AE that fulfills 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event. Important medical events that may not be one of the above may be considered an SAE by the Investigator when, based upon appropriate medical judgment, they are considered clinically significant and may jeopardize the participant, or may require medical or surgical intervention to prevent one of the outcomes listed above.

An AE is considered "life-threatening" if, in the opinion of either the Investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

7.1. Eliciting and Documenting Adverse Events

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).

Laboratory test values or investigational findings (eg, findings on ECGs, imaging, or examination) outside the normal reference range that meets the following criteria should be reported as an AE:

1. Is confirmed and the Investigator considers clinically significant, or
2. Requires a participant to be discontinued from the study, or
3. Requires a participant to receive treatment.

Abnormal laboratory test values or investigational findings reported as AEs should be followed until satisfactory clinical resolution, participant withdrawal of consent, loss to follow-up, or death, whichever comes first.

7.2. Reporting Adverse Events and Serious Adverse Events

All AEs and SAEs must be recorded and reported to the Sponsor (if applicable) from the time of informed consent through EOS, regardless of cause or relationship.

After EOS, any unresolved AEs and/or SAEs will be followed up through to resolution, return to baseline condition, or until participant is lost to follow-up or dies of another cause. Additionally, SAEs considered related to study treatment that occur at any time should be reported by the Investigator regardless of the AE/SAE collection window. SAEs considered related and

unexpected (SUSAR) will be reported as required by local as well as country-specific regulatory bodies as well as to Eudravigilance based on the Eudravigilance Implementation guidelines. Definitions describing what is and is not considered an AE are provided in Section 7.

In the event of any SAE reported or observed during the study, the investigational site is required to complete the AE eCRF within the EDC system, indicating the AE is serious, within 24 hours of becoming aware of the event or aware of new information relating to the event.

In the event that the EDC system is not available, a paper SAE Report Form should be used and emailed to drugsafety@alector.com, according to the instructions provided in the Study-specific Regulatory Binder. Information to be collected includes the following:

- Event term
- Date and time of onset of event
- Investigator-specified assessment of severity and relationship to study drug
- Date and time of resolution of the event
- All applicable seriousness criteria
- Any required treatment or evaluations
- Event outcome

The participant's condition will be followed up by the Investigator or designated subinvestigator until resolution of the condition, as described in Section 7.6. If additional visits are required, the participant will be asked to return to the investigational site for further follow-up. As additional information becomes available, such as hospital discharge notes and participant medical records, the Investigator or designee will update the AE eCRF and other relevant documentation pertaining to the SAE, and these updates will be submitted to the Sponsor within 24 hours of knowledge.

- Alector will be responsible for notifying the applicable regulatory agencies of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. In addition, Alector must notify the applicable regulatory agencies and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any source, as soon as possible, but in no case later than 15 calendar days after Alector determines that the information requires reporting.
- It is the Investigator's responsibility to report all SAEs to Alector in compliance with the protocol and to send SUSAR reports to their IRB or Local Ethics Committee per institutional guidelines and local requirements.

The Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or later will be used by Alector to code all AEs.

7.3. Protocol-specific Disease Progression Adverse Event and Serious Adverse Event Reporting Requirements

Disease progression in this study is measured by the clinical co-primary efficacy endpoint (CDR® plus NACC FTLD) and other cognitive and functional assessments. Changes in these scores that are consistent with the expected rate of progression of the underlying disease should not be recorded as AEs.

However, symptomatic deterioration or events that are judged by the Investigator to be inconsistent with normal disease progression or are considered related to study treatment should be reported as AEs, and if any of the "serious" criteria are met, it must be reported as an SAE.

Please note that the term "disease progression" should not be reported, but rather the clinical manifestation(s) with applicable descriptors should be captured on the Adverse Event eCRF page.

7.4. Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the participant's daily activities. Severity will be graded according to the WHO Toxicity Grading Scale, Mar 2019 or later. If an AE is not specified within the WHO Toxicity Grading Scale, then the AE will be graded according to the following definitions:

Grade	Severity	Description
1	Mild	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The participant may be aware of the sign or symptom but tolerates it reasonably well.
2	Moderate	Mild to moderate limitation in activity; no or minimal medical intervention/therapy required.
3	Severe	Marked limitation in activity; medical intervention/therapy required; hospitalizations possible.
4	Life-threatening	The participant is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.
5	Death	Any AE where the outcome is death.

Note that the term "severe" is a measure of intensity, and that a severe AE is not necessarily serious.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. AEs characterized as intermittent do not require documentation of onset and duration of each episode. When the severity of an AE changes more than once a day, the maximum severity for the event should be listed. If the severity changes over a number of days, these severity changes should be recorded separately (ie, as having distinct onset dates).

7.5. Assessment of Causality

The relationship or association of the study treatment in causing or contributing to the AE will be characterized using the following classification and criteria:

Relationship to Study Treatment	Comment
Related	There is reasonable possibility that the event may have been caused by study treatment (eg, confirmation by positive rechallenge test).
Not Related	The event can be readily explained by the participant's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and study treatment.

The Investigator should assess causality by answering either "related" or "not related" to the question, "Is there a reasonable possibility that the event may have been caused by the study treatment?"

The following factors may be used in consideration of causality assessment:

- Challenge/rechallenge: Did the event abate after study treatment was reduced or interrupted? Did the event reappear after study treatment was reintroduced?
- Temporal relationship and time to onset plausibility
- Confounding risk factors
- Amount and duration of study treatment exposure
- Concomitant medications

7.6. Follow-up of Participants Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF. The Investigator should follow each AE and SAE through satisfactory clinical resolution.

All AEs and SAEs that have not resolved by the end of the study or that have not resolved upon discontinuation of the participant's participation in the study must be followed up until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value is available
- The participant withdraws consent
- The participant dies
- The event can be attributed to agents other than the study treatment, or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

After the protocol-defined follow-up period, if the Investigator becomes aware of any SAE assessed as related to an Alector investigational drug, the SAE must be reported to Alector within 24 hours of site awareness.

7.7. Infusion Reactions

Signs or symptoms of AEs during the infusion will be carefully monitored and treated according to institutional guidelines. Further details regarding infusion-related reactions are provided in Section 5.3.2 of this protocol and in the AL001 IB.

7.8. Anaphylaxis

Signs or symptoms of anaphylaxis will be carefully monitored and treated according to institutional guidelines. Emergency crash cart equipment and medications, including multiple doses of epinephrine, pressors, and bronchodilators, will be available at all times during the infusion portions of the study.

7.9. Special Situations

Special situations are nonstandard medical conditions that provide valuable information about an investigational product and therefore should be reported. All special situations associated with an AE or SAE should be recorded in the EDC system in the AE eCRF. Special situations associated with AEs or SAEs must be reported within 24 hours of becoming aware of the special situation.

Special situations are defined as below:

- Overdose: This refers to the administration of a quantity of investigational product (IP) given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied.
- Misuse: This refers to situations where the IP is intentionally and inappropriately used not in accordance with the prescribed or authorized dose, route of administration, and/or the indication(s) or within legal status of its supply.
- Medication error: A medication error is any dose of study treatment given to a participant or taken by a participant that differs from the dose/volume of prepared dose/duration of infusion described in the protocol. Medication errors are not likely in the study, as the study treatment is administered by IV infusion by trained personnel under the supervision of the Investigator or their designee.
- Occupational exposure: This corresponds to an IP for human use as a result of one's occupation.

7.10. Pregnancy

Female participants must be instructed to discontinue all study treatments and inform the Investigator immediately if they become pregnant during the study.

The Investigator must report any pregnancy that occurs in a female participant or partner of a male participant within 24 hours of becoming aware of it by submitting the Pregnancy Report Form. Follow-up information documenting the pregnancy outcome should be reported on the Pregnancy Report Form. The investigational site should email the Pregnancy Report Form to drugsafety@alector.com, according to the instructions provided in the Study-specific Regulatory Binder.

All pregnancies must be reported on the appropriate page in the eCRF.

Pregnancies are captured if they occur in female participants or in the sexual partners of male participants from the time the participant is first exposed to the study treatment until Part1/Part 2 EOS or Safety Follow-up visit, whichever is later.

An uncomplicated pregnancy will not be considered an AE or SAE, but all pregnancies will be followed-up through term.

Any congenital abnormalities noted at birth in the offspring of a participant who received study drug or in the sexual partner of a male participant who received study drug will be reported as an SAE. The outcome of any pregnancy and the presence or absence of any congenital abnormality will be recorded in the source documentation and reported using the Pregnancy Report Form.

Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the participant has completed the study, and considered by the Investigator as possibly related to the study treatment, must be promptly reported to Alector.

7.10.1. Breastfeeding

Adverse events that occur in infants following exposure to an IP from breast milk should be reported.

8. STATISTICAL METHODS AND ANALYSIS PLAN

This protocol describes the statistical analysis as it is foreseen at the time of this protocol amendment. A fully detailed statistical analysis plan (SAP) will be finalized prior to any planned analysis. A separate SAP will be drafted for the OLE portion of the study and finalized prior to database lock of the OLE. All SAPs serve as a complement to the protocol and supersede it in case of differences. Any deviations from the statistical analyses planned will be documented in the final clinical study report.

8.1. General Considerations

All data for each participant will be listed as collected. All statistical summaries and analyses will be performed using Statistical Analysis System (SAS) software (SAS Institute, Cary, North Carolina, US).

Continuous data will be summarized using an 8-point descriptive summary (n, mean, standard deviation, median, interquartile range [25% quartile, 75% quartile], minimum, and maximum) unless otherwise specified in the SAP or table shell. Categorical data will be summarized using counts and percentages.

For analysis, Day 0 is defined as the day of the first study medication dose. The preceding day is Day -1.

Baseline is the last assessment (scheduled or unscheduled) obtained before start of study medication dosing, unless otherwise specified in the SAP. Baseline for endpoints that have more than 1 component is calculated from the individual component baselines, whether or not they were assessed during the same visit.

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in the SAP. Any changes to the data summaries and analyses outlined in this section will be documented in the SAP. Additional statistical analyses other than those described in this section may be performed if deemed appropriate. Any deviations from the analysis planned in the SAP will be justified and recorded in the final clinical study report (CSR).

The study endpoints are provided in Table 1.

8.2. Sample Size Calculations - Part 1

The study was designed to enroll both symptomatic participants with a CDR® plus NACC FTLD-SB score >0.5 and pre-symptomatic/at-risk participants with a CDR® plus NACC FTLD-SB score ≤0.5 with an elevated serum NfL. At the initial design stage of the trial, data from the GENFI registry were analyzed to obtain an estimate of the expected change over time in the clinical co-primary endpoint CDR® plus NACC FTLD-SB, and its associated variability, in the at-risk and symptomatic participants for the purpose of sample size estimation. This analysis showed the 2-year coefficient of variation (CV) for the change in the CDR® plus NACC FLTD-SB was 77% for the symptomatic cohort and 165% for the at-risk cohort.

Following a recommendation from the FDA during the review of the draft AL001-3 SAP, the study objective was changed to include plasma PGRN as a biomarker co-primary endpoint. As a result of this change, a post hoc power calculation was performed to ensure that there was still sufficient power for this study to support the inclusion of plasma PGRN as a co-primary

endpoint. Based on available data from AL001-2 for symptomatic FTD-GRN participants treated with AL001, it is expected that after 96 weeks of treatment, participants would experience a mean (SD) of the change from baseline of log-10 transformed plasma PGRN concentration of 0.45 (0.0815). Based on longitudinal data from a large observational cohort of FTD patients (Sellami 2020), plasma PGRN levels are low and stable throughout the course of the disease up to 10 years following disease onset. As a result, plasma PGRN levels are not expected to change over 96 weeks while on placebo. Therefore, the change from baseline of log-10 transformed plasma PGRN concentration for the placebo arm is assumed to be 0, with a common SD of 0.0815 to match the AL001-treated participants. Anticipating that there may be as many as 63 participants with a baseline and week 96 plasma PGRN concentration, in a 2:3 allocation ratio of placebo:AL001, a two-sample t-test shows that there is >99% power at a 1-sided 2.5% significance level to detect the treatment difference. Therefore, there is adequate power in this study to detect a treatment effect on both the clinical co-primary endpoint and the biomarker co-primary endpoint.

Based on the small number of at-risk participants who have enrolled and routine blinded monitoring of the accumulating INFRONT-3 data, which has indicated a lack of progression in the at-risk participants thus far, the primary analysis population was changed to focus on the symptomatic participants. It is estimated that for a primary analysis based on the symptomatic population only, 90 participants would be required to achieve at least 85% power (with 1-sided 2.5% significance level) to detect a 40% slowing in the AL001 treatment group, relative to the placebo group, assuming the 96-week CV is 65% and the 48- and 96-week dropout rates are 30% and 40%, respectively. The new proposed sample size (N=90 symptomatic participants) is based on the observed 2-year variability (CV=68%) from the GENFI and ALLFTD registries reported by Staffaroni (Staffaroni 2022). A slightly smaller variability (65%) has also been assumed due to routine blinded monitoring of the accumulating INFRONT-3 data.

8.3. Analysis Sets

8.3.1. All Randomized Set

The All Randomized set includes every randomized participant.

8.3.2. Full Analysis Set

The FAS will consist of all symptomatic and at-risk participants who are randomized and receive any portion of double-blind study treatment. Efficacy analyses will be analyzed according to the randomized treatment group. This analysis set will be used for some supportive modeling for the co-primary endpoints and selected secondary endpoints (CGI-S, CGI-I, and FRS).

8.3.2.1. Full Analysis Set-symptomatic (FAS-symptomatic)

This set will consist of the subset of symptomatic participants from the FAS population. This analysis set will be used for both co-primary analyses, the secondary efficacy analyses and exploratory biomarker analyses. This analysis set will be used for some supportive modeling for the co-primary endpoints and selected secondary endpoints (CGI-S, CGI-I, and FRS).

8.3.2.2. Full Analysis Set-at Risk (FAS-at Risk)

This set will consist of the at-risk participants from the FAS population. These will be used to support descriptive summaries only due to the small number of at-risk participants that enrolled in the study.

8.3.3. Per-protocol Analysis Set (PPS)

The PPS will consist of all participants in the FAS-symptomatic without any major protocol deviation that would impact the assessment or interpretation of efficacy. All major protocol deviations will be reviewed and agreed on prior to database lock. This analysis set will be used for supportive efficacy analyses of the co-primary and secondary efficacy endpoints.

8.3.4. Safety Set

The Safety set will include all participants in the FAS set. This analysis set will be used for the primary safety analyses. Further safety analyses may be conducted separately by symptomatic status. Safety analyses in Part 1 will be analyzed according to the actual treatment they received, rather than as randomized. If a participant is randomized to AL001 in Part 1 and receives any amount of AL001 in Part 1, they will be included in the AL001 group. If a participant is randomized to placebo in Part 1, and receives any amount of AL001 in Part 1, they will be included in the AL001 group.

8.3.5. Pharmacokinetic (PK) Set

The PK set will be used for PK summaries and will include all participants in the Safety set who had adequate assessments for determination of at least 1 PK parameter. This analysis set will be used for all PK parameter analyses.

8.4. Subgroups Analyses

The clinical co-primary endpoint and secondary endpoints will be summarized by the following subgroups based on the FAS-symptomatic:

- Age
- Sex
- Race
- Clinical phenotype (bvFTD vs. PPA)
- Geographical region
- Baseline CDR® plus NACC FTLD Global Score (<2 vs. =2) in the symptomatic subgroup

The co-primary biomarker endpoint (plasma PGRN) will be summarized in the subgroups of age, sex, and baseline CDR® plus NACC FTLD Global Score based on the FAS-symptomatic.

With respect to analysis of the clinical co-primary efficacy, biomarker co-primary and secondary efficacy endpoints in the subgroups, this study is not statistically powered to detect the prespecified treatment effect in any subgroups.

Other subgroup analyses may be performed and will be specified in the SAP.

8.5. Statistical Analysis Methodology

8.5.1. General Analyses

Unless specified otherwise, general analyses will be applied to All Enrolled, FAS-symptomatic, and Safety set.

8.5.1.1. Disposition of Participants

Disposition will be summarized, presenting the numbers of participants, reasons for study discontinuation, and reasons for study treatment discontinuation.

8.5.1.2. Protocol Deviations

A protocol deviation occurs when the participant, Investigator, or Alector (or designee) fails to adhere to protocol requirements. Major protocol deviations for this study are described in Section 12.2.2.

Major protocol deviations will be summarized, and all protocol deviations will be listed, including the categorizations of deviations as major or minor.

8.5.1.3. Demographics and Other Baseline Characteristics

Demographics (including but not limited to age, sex, race, ethnicity, and handedness, if allowable per local regulatory authorities) and other baseline characteristics will be summarized.

8.5.1.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO-DD, Mar 2020 or later.

A medication will be considered as "prior" if the stop date and time of administration are before the start of the first study treatment administration on Day 0. A medication will be considered "concomitant" if the stop date and time of administration is after the start of study treatment administration. If the date and time of administration contains partial information such that the attribution of concomitant administration cannot be ruled out, then it will be considered concomitant. A medication started before study treatment and continuing during the study will be considered concomitant.

All prior and concomitant medications data will be summarized by anatomical therapeutic chemical class (ATC) and generic name. Prior and concomitant medications will be summarized separately.

8.5.2. Analyses of Efficacy Endpoints

The FAS-symptomatic is the primary analysis set for efficacy analyses and summaries. The primary analysis of all efficacy endpoints will include all data collected during the trial, irrespective of whether a participant discontinues study treatment or takes a prohibited medication. This is aligned to an estimand based on the Treatment Policy strategy for discontinuations from treatment/and use of other prohibited medications. The trial has been designed to follow all participants randomized, irrespective of whether they discontinue study

treatment, and to collect all COA assessments until Part1/Part 2 EOS or Safety Follow-up visit, whichever is later.

8.5.2.1. Clinical Co-primary Efficacy Endpoint

The primary analysis will use a proportional MMRM (pMMRM) approach (Wang 2022). A pMMRM models the treatment effect as a single proportional difference at each post-baseline visit. Because greater noise than signal is expected in the early stages of the trial, the pMMRM model will only assume the treatment effect is proportional from Week 48 through Week 96, and use the time points of Weeks 48, 72, and 96 to estimate the treatment effect (θ). Further details about imputation and missing data handling rules will be described in the SAP.

The following superiority hypothesis will be tested using a 1-sided 2.5% significance level:

- H0 (null): $\theta \leq 0$, indicating that treatment does not slow disease progression relative to placebo control.
- H1 (alternative): $\theta > 0$, indicating that treatment slows disease progression relative to placebo control.

Supportive analyses of the clinical co-primary endpoint will focus on model specification using the FAS-symptomatic set. These analyses will consider alternative analysis models, including the MMRM and linear mixed effect models. A supportive analysis using MMRM analysis model with the PPS set may also be conducted as a supportive analysis.

Full details of the supportive and sensitivity analyses for the clinical co-primary endpoint will be provided in the SAP.

8.5.2.2. Biomarker Co-primary Endpoint: Plasma Progranulin

The biomarker co-primary endpoint will use change from baseline of the log-10 transformed plasma PGRN concentration at Week 96. All change from baseline values up to Week 96 will be included in the model.

Analysis values for plasma PGRN concentrations will be used. If necessary, values below or above quantitation limits will be imputed based on the description provided in the SAP. The change from baseline of the log-10 transformed values will be used for analysis. Missing concentration values will not be imputed.

This analysis will use the FAS-symptomatic and will be conducted using the MMRM model for the change from baseline in log-10 transformed plasma PGRN concentration.

The hypothesis to be tested for the biomarker co-primary (based on the MMRM model) will be using a 1-sided 2.5% significance level as follows:

- H0 (null): $\Delta = 0$, indicating that the change from baseline at Week 96 in treatment group is the same as that of the placebo group.
- H1 (alternative): $\Delta > 0$ for plasma PGRN, indicating a treatment benefit favoring AL001.

8.5.2.3. Secondary Efficacy Endpoints

All secondary endpoints (CGI-I, CGI-S, FRS, RBANS) will be analyzed using the same pMMRM approach as the clinical co-primary efficacy endpoint, using the FAS-symptomatic analysis set. Analyses of secondary endpoints will be described in the SAP, along with full details of the supportive and sensitivity analyses.

8.5.2.4. Exploratory Endpoints

Analyses of exploratory endpoints will be described in the SAP.

8.5.2.5. Multiplicity Adjustment

Interpretation of inferential analyses and adjustments for multiplicity for secondary endpoints will only be made if success is declared for the co-primary endpoints. If the primary hypothesis for both co-primary endpoints is rejected at the one-sided 0.025 level, the remaining endpoints will be tested in sequential order as follows: CGI-S, FRS, CGI-I, and RBANS at one-sided 0.025 level. During the testing, if any endpoint fails to be rejected at the 0.025 level, the testing procedure will stop, and for all subsequent endpoints only nominal p-values will be reported.

8.5.3. Analysis of Safety

The primary analysis population for all safety assessments will be the Safety set. Safety analyses will also be conducted separately by symptomatic status at baseline.

8.5.3.1. Study Treatment Administration

Study treatment administration data will be summarized by number of doses received and total mg/kg received. The overall treatment compliance will be calculated accounting for dose interruptions and discontinuations.

8.5.3.2. Adverse Events

AEs will be recorded as described in Section 7.2 and coded to system organ class (SOC) and preferred term (PT) according to MedDRA Version 22.0 or later. A TEAE is defined as described in Section 7. The following categories of AEs will be summarized by SOC, PT, and symptomatic (yes/no) at baseline:

- TEAEs
- Treatment-related TEAEs
- TEAEs by relationship to study treatment
- TEAEs by intensity
- SAEs
- TEAEs leading to study treatment discontinuation
- TEAEs leading to study discontinuation
- TEAEs leading to death

For safety reporting, any clinically significant changes in MRI after dosing relative to baseline will be evaluated by the Investigator and will be included in the eCRF as AEs. AEs identified through MRI will not be analyzed separately.

8.5.3.3. Physical and Neurological Examinations

Clinically significant findings from physical and neurological examinations will be recorded as AEs and, therefore, no separate summary will be prepared.

8.5.3.4. Vital Signs and Weight Analysis

For vital signs and weight, values at visits and changes from baseline will be summarized at each post-baseline visit.

8.5.3.5. Electrocardiogram Analysis

For quantitative ECG results, values at visits and changes from baseline will be summarized at each post-baseline visit. A shift table will be generated for the categorical interpretations of ECGs. Any Grade 3 or higher Fridericia-corrected QT (QTcF) interval prolongations will be listed.

ECGs being read centrally will be analyzed and reported in a separate report.

8.5.3.6. Clinical Laboratory Analytes

Values at visits and changes from baseline in clinical laboratory analytes will be summarized at each visit. Shift tables will be generated for these analytes, showing the number of participants with low, normal, or high values at baseline and each post-baseline visit and the endpoint value according to the local laboratories' reference ranges.

8.5.3.7. Sheehan-Suicidality Tracking Scale

Sheehan-STS total scores will be summarized by visit.

8.5.3.8. Immunogenicity Test

Immunogenicity test results for ADAs to AL001 will be summarized by time point.

8.5.4. Analyses of Pharmacokinetic, Pharmacodynamic and Disease Biomarker Endpoints

8.5.4.1. Pharmacokinetic Endpoints

All PK summaries will be presented using the PK set.

Mean serum AL001 concentration time data will be tabulated and plotted by study day and whether symptomatic (yes/no). The following serum PK parameters will be estimated by standard noncompartmental methods using Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey, USA) Version 8.0 or higher: maximum observed concentration (C_{max}), trough concentration (C_{trough}), and area under the concentration time curve at steady state (AUC_{ss}) (if data allow) following multiple doses of AL001.

PK parameters will be summarized using the following descriptive statistics: n, arithmetic mean, SD, CV, geometric mean, geometric mean CV, minimum, median, and maximum. Geometric mean, 95% confidence interval (CI), and CV will only be included for C_{max}, C_{trough}, and AUC_{ss}.

Potential correlations of relevant PK parameters with demographics, safety (including QT changes), and biomarker measures may be explored, as data allow. Additional modeling, including population PK analysis, to characterize these correlations may be performed. The results of such additional analyses may be reported separately from the CSR.

8.5.4.2. Pharmacodynamic and Disease Biomarker Endpoints

PD and disease biomarker summaries will be presented using the FAS-symptomatic and FAS-at risk.

Biomarker endpoints include but are not limited to, blood and CSF PGRN and NfL, and MRI brain volume images.

Summary statistics for biomarker endpoints of absolute value, changes, and percent change from baseline will be tabulated by study day and whether symptomatic (yes/no) on the original scale and natural log-transformed scale, if applicable. The time course of biomarker endpoints may be presented graphically for both observed values at the individual participant level, as well as by arithmetic mean ± SE, and/or geometric mean ± SE. In addition, an MMRM may be used to summarize the mean percent changes in biomarker endpoints from baseline with 95% CIs. Association between biomarker endpoints and clinical response will be explored.

The PK-PD relationship may be modeled by a population PK/PD model using nonlinear mixed effects modeling. Baseline biomarkers may also be explored as potential predictors of response to AL001, including baseline plasma or CSF PGRN levels, and serum or CSF NfL levels.

Full details of PD and disease biomarker analyses will be described in the SAP.

8.5.5. Interim Analyses

There is no planned interim analysis for Part 1 or Part 2 of this study.

9. DATA QUALITY ASSURANCE

This study will be conducted according to the International Council for Harmonisation (ICH) E6(R2) risk and quality processes described in the applicable procedural documents. The quality and risk management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management.

All aspects of the study will be monitored for compliance with applicable government regulatory requirements, current Good Clinical Practice (GCP), the protocol, and applicable SOPs. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and site personnel. eCRFs and EDC will be used. The EDC system is validated and compliant with US Title 21 Code of Federal Regulations (CFR) Part 11. Each person involved with the study will have an individual identification code and password that allows for record traceability. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

9.1. Data Management

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the participants treated as part of the research under this protocol. The Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, recorded data from automated instruments, medical progress notes, email correspondence, and ECG strips. In addition, electronic COA devices will be used to capture the COAs. This will be part of the source. An application on a tablet device will be used for the optional WLAs. All data collected by the Winterlight application will be stored securely on the device during assessment administration and uploaded directly to Winterlight's secure servers upon assessment completion.

The Investigator will adhere to Good Documentation Practice and investigative site personnel will enter participant data into the eCRF. The Investigator agrees to periodic review of eCRFs for each study participant. The analysis datasets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable standards and will include data cleaning procedures to ensure the integrity of the data, eg, identifying errors and inconsistencies in the data. Adverse event terms will be coded using the MedDRA Version 23.0 or later, an internal validated medical dictionary, and concomitant medications will be coded using the WHO-DD, Mar 2020 or later.

After database lock, each investigational site will receive a digital file containing all of their site-specific eCRF data as entered into the EDC system for the study, including full discrepancy and audit history. Additionally, a digital copy of all of the investigational site's data from the study will be created and sent to Alector for storage. Alector will maintain a duplicate digital file copy for their records. In all cases, participant initials will not be collected or transmitted to Alector.

9.2. Data Protection

Alector will ensure that any collection and processing of personal data within the scope of and for purposes of this study will be carried out in compliance with applicable data protection laws, including the European General Data Protection Regulation 679/2016.

Alector implements and maintains organizational and technical measures designed to protect personal data and avoid unauthorized access, disclosure, dissemination, alteration, or loss of information and processed personal data. Such organizational and technical measures include, but are not limited to, physical access controls including monitoring of physical access, security locks, security guards, automated access controls, such as badges, visitor approval; encryption and pseudonymization of data (where appropriate); restricted user access relevant to the function and type of activity performed in relation to the clinical trial; audit controls and procedures to maintain integrity and protection of personal data; ability to ensure the ongoing confidentiality, integrity, availability, and resilience of processing systems and services; network, system, and application security by means of access rights management, logging of access, antivirus/anti-malware protection and firewalls, and other security measures; ensuring detection of malware purposed for unauthorized deletion, blocking, copying of information, disabling security measures, and response to such attacks; transfer and disclosure controls and protections; means to restore the availability and access to personal information in a timely manner in the event of a physical or technical incident; logging of security events/incidents in information systems; procedures to detect within timely manner if a personal data breach has occurred and incident response plan and procedures for investigation, containment, reporting and resolution of incidents; backup procedures and business continuity plans and procedures; a process for regularly testing, assessing, and evaluating the effectiveness of technical and organizational measures for ensuring the security of the processing; and security and training awareness for employees and personnel managing clinical studies.

All locations, personnel, and information systems that are used to perform services for the study will be covered. In addition, Alector will ensure the technical and organizational security measures described above, are regularly reviewed and updated to consider technological developments.

Alector and its selected vendors working on behalf of Alector or institutions working with Alector for purposes of the study are contractually bound to protect confidentiality of records and coded personal data of the clinical subjects, and Alector has implemented appropriate internal safeguards and controls to protect the confidentiality of records and personal data of study subjects, including by appropriate access rights management on a need-to-know basis and confidentiality undertakings for personnel involved in the handling of study subject data. Alector will only receive coded (pseudonymized) personal data of clinical subjects with the code being allocated and held by the sites for each study subject. The relevant codes and attribution tables will be kept confidential, and coded (pseudonymized) data will be used instead of direct identifiers in all materials associated with the study participant. Alector will neither receive nor request any information to attribute any coded data to any individual study subjects, except as necessary in the context of activities required to comply with applicable laws and/or the regulatory clinical trial framework, including for purposes of (on-site) monitoring, inspections and/or regulatory audits. Alector will only share participant coded data as described in the ICF.

Alector has implemented operational data breach response processes for responding to any data breach occurring at facilities and premises of Alector, its vendors, or institutions working with Alector, as required under applicable data protection laws. In case of the occurrence of any data breach, Alector will apply relevant measures to mitigate the risks to data subjects as appropriate in relation to the specific context of the data breach, considering its source, underlying intentions, possibilities of recovery, etc. Any data breach presenting risks to the rights and freedoms of data subjects will be reported to data protection authorities and/or data subjects in accordance with the requirements and timelines set forth under applicable data protection laws.

10. ETHICS

10.1. Independent Ethics Committee or Institutional Review Board

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human participants in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study participants, and any other written information regarding this study to be provided to the participant or the participant's legally authorized representative must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): GCP will be maintained by the investigational site and will be available for review by Alector.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The Investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The Investigator must promptly supply Alector, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to participants.

10.2. Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, the protocol, and all applicable regulations.

10.3. Participant Information and Consent

A written ICF in compliance with US Title 21 CFR Part 50 and any other applicable regulatory authority regulations shall be obtained from each prospective participant before entering the Part 1 treatment period of the study, before continuation of treatment in the optional Part 2, or performing any unusual or nonroutine procedure that involves risk to the participant. An ICF template may be provided by Alector to investigational sites. If any site-specific modifications to study-related procedures are proposed or made by the investigational site, the ICF should be reviewed by Alector before IRB/IEC submission. Once reviewed, the ICF will be submitted by the Investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participants and study partners must sign the revised ICF.

Before recruitment and enrollment into Part 1 and Part 2, each prospective participant will be given a full explanation of the study and be allowed to read the approved ICF. Once the Investigator is assured that the prospective participant understands the implications of participating in the study, the prospective participant will be asked to give consent to participate in the study by signing the ICF.

FTD is a rare neurodegenerative condition that is characterized by progressive deterioration of cognitive and/or language abilities. As such, it is important to provide mechanisms for participants who may have marked deficits in their cognition or language abilities to be able to

participate in the trial. Thus, if the prospective participant is not competent, a legally authorized representative must provide informed consent on their behalf, and the prospective participant must provide assent, in accordance with the local regulations, guidelines, and the IRB/IEC. If the study participant becomes incompetent over the course of the study, a legally authorized representative will need to be identified and the participant will need to provide assent to continue, in accordance with the local regulations, guidelines, and the IRB/IEC.

Before recruitment and enrollment into Part 1 and Part 2, the prospective participant's study partner will be given a full explanation of the study and be allowed to read the approved ICF. Once the Investigator is assured that the prospective study partner understands the implications of participating in the study, the prospective study partner will be asked to give consent to participate in the study by signing the ICF.

FTD is a debilitating and life-threatening progressive neurologic disease with no available treatments to slow or prevent disease progression. Participation in this study may confer a direct benefit to incompetent participants or may provide benefit for the FTD population represented by the incompetent participant concerned, in service of the development of much needed treatments for FTD.

The Investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the participant/legally authorized representative, and study partner.

Consent for Optional Future Research

Prior to agreeing to samples being retained for future testing outside of the main study, participants will provide informed consent in accordance with the SOPs of the investigational site.

Consent for Optional Lumbar Puncture Procedures for CSF Collection

Prior to performing any of the optional lumbar puncture procedures for CSF collection or coagulation sampling, participants will provide informed consent in accordance with the SOPs of the investigational site.

Consent for Optional WLA Assessments

Prior to participating in the optional WLAs, participants and their study partners will provide informed consent in accordance with the SOPs of the investigational sites.

Consent for Optional National Institutes on Aging (NIA) Global Unique Identifier (GUID)

Prior to the investigational site collecting/assigning the optional NIA GUID as described in Section 6.5.3, participants will provide informed consent in accordance with the SOPs of the investigational sites.

Consent for Optional Pre-screening to Confirm Presence of Known Common Genetic Mutations Associated with Frontotemporal Dementia (including GRN Mutations)

Prior to participating in the optional pre-screening to confirm the presence of known common genetic mutations associated with frontotemporal dementia including *GRN* mutations, participants will provide informed consent in accordance with the SOPs of the investigational sites.

Consent for Optional Pre-screening to Confirm Presence of Elevated Serum NfL Levels

Prior to participating in the optional pre-screening to confirm the presence of elevated serum NfL levels, participants will provide informed consent in accordance with the SOPs of the investigational sites.

11. INVESTIGATOR'S OBLIGATIONS

The following administrative items are meant to guide the Investigator in the conduct of the study but may be subject to change based on industry and government SOPs, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

11.1. Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Information pertaining to the participant or the study monitor will not be released without the written permission of the participant (or the participant's legally authorized representative) or the study partner, except as necessary for monitoring and auditing by Alector, its designee, the US FDA/EMA, or the IRB/IEC.

The Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from Alector must be obtained for the disclosure of any said confidential information to other parties.

All personal data collected related to participants, investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in accordance with local data protection law.

Data collected must be adequate, relevant, and not excessive in relation to the purposes for which they are collected. Each category of data must be properly justified and in alignment with the study objectives.

11.2. Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow Alector to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the Investigator must provide to Alector a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Alector is not financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, Alector is not financially responsible for further treatment of the participant's disease.

11.3. Investigator Documentation

Prior to beginning the study, the Investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original investigator-signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572, or an equivalent form capturing this information
- Curriculum vitae for the Investigator and each subinvestigator listed on Form FDA 1572 or equivalent
- Financial disclosure information to allow Alector to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to Alector a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study
- IRB/IEC-approved informed consent, samples of investigational site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the participant or legally authorized representative
- Laboratory certifications and normal ranges for any local laboratories used by the investigational site for this study, in accordance with 42 CFR 493
- Additional documentation may be requested that is not included in the list per local regulatory requirements

11.4. Study Conduct

The Investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial databases.

11.5. Adherence to the Protocol

The Investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

11.6. Adverse Events and Study Report Requirements

By participating in this study, the Investigator agrees to submit reports of SAEs to Alector and/or the IRB/IEC according to the timeline and method outlined in the protocol. In addition, the Investigator agrees to submit annual reports to the investigational site IRB/IEC as appropriate.

After the protocol-defined follow-up period, Alector must be notified if the Investigator becomes aware of any SAE that is believed to be related to the participant’s prior study treatment.

11.7. Investigator's Final Report

Upon completion of the study, the Investigator, where applicable, will inform the institution; the Investigator/institution will provide the IRB/IEC with a summary of the study's outcome, and provide Alector and regulatory authorities with any reports required.

11.8. Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Alector. It is the responsibility of Alector to inform the Investigator/institution as to when these documents no longer need to be retained. The Trial Master File (TMF) will be created during the implementation phase of a study, maintained on an ongoing basis throughout the duration of the project, and collated at the end of the study.

11.9. Publications

After completion of the study, the data will be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, Alector will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. Alector has final approval authority over all issues pertaining to publication of the study results.

Data from this study are the property of Alector and cannot be published without prior authorization from Alector, but data and publication thereof will not be unduly withheld.

12. STUDY MANAGEMENT

12.1. Monitoring

12.1.1. Independent Data Monitoring Committee

An iDMC will be established by the Sponsor to review accumulating study data to monitor the safety of all participants in the double-blind portion of the study on an ongoing basis. Members of the committee will include 2 clinicians and a biostatistician who have experience in the conduct and monitoring of clinical studies. No Alector employee or Investigator involved in the AL001 clinical studies will be a member of the iDMC or participate in closed iDMC sessions; however, representatives from Alector may attend the open meeting sessions and will be able to provide additional information, as requested.

The iDMC will review the progress of the study and perform interim reviews to evaluate potential safety and tolerability issues.

The iDMC will act in an advisory capacity to the Sponsor. The iDMC responsibilities will be detailed in a charter and will include but not be limited to the following:

- Review the following documents before commencing activities as an iDMC: draft iDMC charter, Investigator brochure, study protocols, template ICF, blank case report forms, and data monitoring plans
- Evaluate the progress of the study; timeliness and quality of the data; participant recruitment, accrual, and retention; risk versus benefit to participants; and other factors that might affect the outcome of the study
- Consider relevant information that may have an impact on participant safety or the ethics of the study
- Make recommendations to the Sponsor concerning continuation, termination, or other modifications to the study based on their observations of the study and its data
- Conduct routine review of data according to a preplanned schedule

The iDMC membership and responsibilities will be further outlined in the iDMC Charter, which will be maintained separately from the protocol.

12.1.2. Monitoring of the Study

The clinical monitors, as representatives of Alector, have the obligation to follow the study closely. In doing so, the monitors will visit the Investigator and investigational site at periodic intervals, in addition to maintaining necessary telephone and written contact. The monitors will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and site personnel.

All aspects of the study will be carefully monitored by Alector for compliance with applicable government regulations and with respect to current GCP and current SOPs.

12.1.3. Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the Investigator agrees to allow Alector, representatives of Alector, or a regulatory agency access to all study records.

The Investigator must promptly notify Alector of any audits that have been scheduled by any regulatory authorities. Dependent upon the scope of the regulatory authority audit, Alector may elect to assist the investigational site in preparation or support. The investigation must promptly forward copies of any audit reports received to Alector.

12.2. Management of Protocol Amendments and Deviations

12.2.1. Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the participant, must be reviewed and approved by Alector or its designee. Amendments to the protocol must be submitted in writing to the Investigator's IRB/IEC for approval before participants can be enrolled into an amended protocol.

12.2.2. Protocol Deviations

The Investigator or designee must document and explain in the participant's source documentation any deviation from the approved protocol. The Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study participants without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments will be submitted to the IRB/IEC for review and approval, to Alector for agreement, and to the regulatory authorities, if required.

A protocol deviation occurs when the participant, Investigator, or Alector (or designee) fails to adhere to protocol requirements. Major protocol deviations are those that might significantly affect the completeness, accuracy, and/or reliability of the study data (any primary or secondary endpoints) or that might significantly affect a participant's rights, safety, or well-being. 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 result in a major protocol deviation; Alector will determine if a major protocol deviation will result in withdrawal of a participant from the study

12.3. Study Termination

Although Alector has every intention of completing the study, Alector reserves the right to stop enrollment or discontinue the study at any time for clinical or administrative reasons.

The date the study is completed is defined as the date on which the last participant completes the last visit (includes follow-up visit).

12.4. Clinical Study Report

Whether the study is completed or prematurely terminated, Alector will ensure that the CSR is prepared and provided to the regulatory agencies, as required by the applicable regulatory requirements. Alector will also ensure that the CSR in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of CSRs.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the CSR. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the CSR, Alector will provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study participants, as appropriate. The study results will be posted on publicly available clinical trial databases.

13. REFERENCES

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14. APPENDICES

14.1. Appendix: Schedules of Assessments

Table 3: Schedule of Assessments (Part 1 Treatment Period: Screening Through Week 48)

Procedures[s]	**Pre-screening**[u]	**Screening**	**Treatment Period**												
Visits			**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**
Study week		**-6**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
Visit window (days)				**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Informed consent	x	x													
Demographics[a]		x													
Medical history review		x	x												
Diagnostic characterization[b]		x													
COAs[c]		x							x						x
Review of AEs and concomitant medications[d]		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination[e]		x[e]	x	x	x	x	x	x	x[e]	x	x	x	x	x	x[e]
Neurological examination[f]		x[f]	x	x	x	x	x	x	x[f]	x	x	x	x	x	x[f]
Vital signs and weight[g]		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy test[h,i]		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Sheehan-STS[w]		x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG[j,v]		x	x						x						x
Brain MRI[k]		x													x
Optional lumbar puncture/CSF[l]		x													x
Serology		x													
Blood for pharmacogenomic research[h,m]			x												
Genetic Mutations Associated with Frontotemporal Dementia (including *GRN* Mutations)[u]	x														
Chemistry and hematology[h]		x	x		x		x		x		x		x		x
Coagulation[h,n]		x												x	
Urinalysis[h]		x	x						x						x
ADA serum samples[h,o,p]			x			x			x						x
PGRN plasma samples[h,o]			x		x	x	x		x		x		x		x
NfL serum samples[h,o]	x	x	x		x		x		x		x		x		x

Table 3: Schedule of Assessments (Part 1 Treatment Period: Screening Through Week 48) (Continued)

Procedures[s]	Pre-screening [u]	Screening	Treatment Period												
Visits			**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**
Study week		**-6**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
Visit window (days)				**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Exploratory biomarker plasma samples[h,o]			x		x		x		x		x		x		x
Exploratory biomarker whole blood samples[h,o]			x		x		x		x		x		x		x
PK serum samples[h,o,p]			x		x	x	x		x		x		x		x
Winterlight Labs Speech Assessment (Optional)[t]			x	x	x	x	x	x	x	x	x	x	x	x	x
Randomization[q]			x												
Study treatment administration[r]			x	x	x	x	x	x	x	x	x	x	x	x	x

ADA=antidrug antibody; AE=adverse event; COA=clinical outcome assessment; CSF=cerebrospinal fluid; ECG=electrocardiogram; eCRF=electronic case report form; LP=lumbar puncture; MRI=magnetic resonance imaging; NfL=neurofilament light chain; PGRN=progranulin protein; PK=pharmacokinetic; Sheehan-STS=Sheehan-Suicidality Tracking Scale; V=visit.

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

[b] A diagnostic characterization form will be completed at screening, Week 96, and EOT/EOS for symptomatic participants only. It will also be completed for any pre-symptomatic participant who becomes symptomatic during the course of the study; for these participants, the diagnostic characterization form will be completed at the first visit in which they exhibit clinical symptomatology.

[c] The COAs consist of the Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center frontotemporal lobar degeneration Behavior and Language Domains (CDR® plus NACC FTLD), Frontotemporal Dementia Rating Scale (FRS), Clinical Global Impression-Improvement (CGI-I), Clinical Global Impression-Severity (CGI-S), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), European Quality of Life-5 Dimensions (EQ-5D), Zarit Burden Interview (ZBI), and the Resource Utilization in Dementia-Lite version (RUD-Lite). The CGI-I will not be administered at baseline. The study participant COAs will be performed prior to study treatment administration (if applicable) and prior to any stressful procedures (eg, blood collections, lumbar puncture, imaging). At-risk participants (CDR® plus NACC FTLD-SB score ≤0.5) require the study partner at the COA visits only. At-risk participants who become symptomatic (CDR® plus NACC FTLD-SB score >0.5) during the study treatment period require the study partner at each visit moving forward through the Part1/Part 2 EOS or Safety Follow-up visit, whichever is later.

[d] All AEs and serious AEs (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 treatment that occur at any time should 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 treatment administration (when applicable).

[e] A complete physical examination (PE) will be performed at screening, at Weeks 24, 48, 72, 96 and at EOT/EOS/Safety Follow-up (prior to study treatment administration). A symptom-directed examination is required at all other specified time points. For visits with study treatment administration, the PE should be performed prior to the infusion. The examination will be performed by a physician or by a nurse practitioner or physician's assistant under the supervision of a physician. Complete PEs will include 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 the opinion of the health care provider. Symptom-directed examinations should include cardiovascular, respiratory, and gastrointestinal systems plus any other pertinent system as required. Height (cm) will be measured at screening. Record abnormalities observed at screening on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the AE eCRF.

[f] A complete neurological examination will be performed at screening, at Weeks 24, 48, 72, 96 and at EOT/EOS/Safety Follow-up (prior to study treatment administration). A symptom-directed examination is required at all other specified time points. For visits with study treatment administration, this should be performed prior to the infusion. A complete neurologic examination should include the evaluation of consciousness, orientation, cranial nerves, motor and sensory system, coordination and gait, and reflexes. A 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 eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the AE eCRF.

[g] Vital signs will be recorded as per standard institutional practice. 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 (pre-dose only) at the same visits that vital signs are taken.

[h] Samples will be collected prior to study treatment administration (if applicable).

[i] 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.

[j] Triplicate 12-lead ECGs will be obtained after the participant has been in the supine position for at least 5 minutes. Additional ECG monitoring must be performed during the treatment period, if clinically indicated. On specified dosing days, the ECG will be obtained prior to study treatment administration and within 60 minutes after the end of infusion.

[k] Magnetic resonance imaging scans of the brain will be performed and centrally reviewed for assessment of safety and for evaluation of global and regional brain volumes, volume of white matter hyperintensities (measured by volumetric MRI); brain perfusion (measured by arterial spin labeling MRI); and fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity (measured by diffusion-tensor imaging). During study treatment, MRI is to be performed within ±7 days of a treatment visit and prior to study treatment administration (if applicable). If an MRI and an LP are performed in the same visit, either (a) the MRI should be performed first or (b) the MRI should be performed at least 3 days after the LP. This minimizes the effect of CSF removal on brain volume measurements.

[l] **Optional** CSF samples will be collected via lumbar puncture prior to study treatment administration (if applicable). Any treated participant who has consented to the optional lumbar puncture assessment and discontinues prematurely should have CSF drawn, unless CSF has been drawn within 12 weeks of discontinuation.

[m] This sample should be collected at the baseline visit but may be collected at any time during the study, if necessary.

[n] The coagulation panel will only be assessed at the screening visit and Week 44 visit **only** for participants who have consented to optional CSF sampling.

[o] Details on timing of PK serum samples, ADA serum samples, PGRN plasma samples, serum NfL samples, exploratory biomarker plasma samples, and exploratory biomarker whole blood samples are provided in Table 5.

[p] Blood serum samples will be collected for determination of ADA. In the event of an infusion reaction, a sample of blood should be obtained for PK serum and ADA assessment of AL001 or placebo, and testing should be performed for c-reactive protein, tryptase, and interleukin 6.

[q] Participants will be randomly assigned to receive AL001 (60 mg/kg) or placebo on or prior to Day 0 using a 3:2 allocation ratio, with randomization being stratified by disease severity defined by the CDR® plus NACC FTLD-SB score ≤0.5; CDR® plus NACC FTLD global score 0.5 (with a CDR® plus NACC FTLD-SB >0.5); CDR® plus NACC FTLD global score 1; CDR® plus NACC FTLD global score 2. Randomization will occur before study treatment administration, after all inclusion criteria have been met.

[r] Study treatment administration on Day 0 will not occur until all baseline assessments are completed.

[s] If the assessment is unable to be performed at the scheduled visit, the assessments may be performed remotely or at a future on-site visit with approval from the Medical Monitor. Refer to Section 6.4 for additional details on trial adaptations when on-site visits cannot be performed, or when a participant is nonverbal.

[t] Winterlight Labs Speech Assessments (WLA) (for participants and study partners who are proficient in English, Spanish, French, Dutch, or German and who agree to participate in the optional assessments only) will be conducted at home. Assessments are conducted at home within 7 days prior to study treatment administration 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.

[u] Participants may be pre-screened to determine the presence of *GRN* mutations. If pre-screening is required, the participant must provide informed consent for the pre-screening assessment of the presence of *GRN* mutations and other known common genetic mutations associated with frontotemporal dementia, with genetic counseling highly recommended. In addition, participants may be pre-screened to determine if their serum NfL level is elevated. If pre-screening is required, the participant must provide informed consent for the pre-screening assessment of the serum NfL levels. Elevated serum NfL levels obtained ≤90 days prior to study treatment administration can be used to satisfy eligibility.

[v] Triplicate ECG tracings from Week 0 (pre-dose and post-dose), Week 24, and Week 48 for approximately 60-80 consecutive participants will be read by a core ECG laboratory (Note: Central ECG reads may not occur in real time; thus, these results will not be used for safety assessments during study conduct). Results from centrally read ECG's will not be captured in the eCRF.

[w] If the participant cannot complete the Sheehan-STS evaluation, a clinical evaluation of suicide risk should be completed by a medically qualified staff member. The completion and outcome of this assessment should be recorded in the eCRF and documented in the participant's source documents.

Note: Unscheduled visits may occur at any time while the participant is enrolled in the study. Assessments should be performed as clinically indicated.

Table 4: Schedule of Assessments (Part 1 Treatment Period: Week 52 Through Week 96)

Procedures[q]	**Treatment Period**												**Part 1 EOS[b,t]**	**Part 1 EOT[s]**	**Safety Follow-up[a]**
Visits	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25[b]**			
Study week	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**			
Visit window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Diagnostic characterization[c]												x	x	x	
COAs[d]						x						x	x	x	
Review of AEs and concomitant medications[e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination[f]	x	x	x	x	x	x[f]	x	x	x	x	x	x[f]	x[f]	x[f]	x[f]
Neurological examination[g]	x	x	x	x	x	x[g]	x	x	x	x	x	x[g]	x[g]	x[g]	x[g]
Vital signs and weight[h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy test[i,j]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Sheehan-STS[u]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG[k]						x						x	x	x	x
Brain MRI[l]												x	x	x	
Optional lumbar puncture/CSF[m]												x	x	x	
Chemistry and hematology[i]			x			x			x			x	x	x	x
Coagulation[i,n]											x				
Urinalysis[i]						x						x	x	x	x
ADA serum samples[i,o,p]						x						x	x	x	x
PGRN plasma samples[i,o]						x						x	x	x	x
NfL serum samples[i,o]						x						x	x	x	
Exploratory biomarker plasma samples[i,o]						x						x	x	x	
Exploratory biomarker whole blood samples[i,o]						x						x	x	x	
PK serum samples[i,o,p]						x						x	x	x	x
Winterlight Labs Speech Assessment (Optional)[r]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Study treatment administration	x	x	x	x	x	x	x	x	x	x	x	x	x[t]		

ADA=antidrug antibody; AE=adverse event; COA=clinical outcome assessment; CSF=cerebrospinal fluid; ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; LP=lumbar puncture; MRI=magnetic resonance imaging; NfL=neurofilament light chain; PGRN=progranulin protein; PK=pharmacokinetic; Sheehan-STS=Sheehan-Suicidality Tracking Scale; V=visit.

[a] A Safety Follow-up visit will be performed 10 weeks following the last dose of AL001.

[b] Participants who complete the Part 1 96-week treatment period (Week 96), 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 100 study treatment administration), will complete the Week 96 visit and continue to Part 2 (Week 100) to receive their next regularly scheduled dose of AL001 according to the OLE administration schedule (continuation from Week 96 to Week 100). 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 96 visit. Study treatment administration will only occur at the Part 1 EOS visit (at the scheduled Week 96 time point) for participants who complete the Part 1 96-week treatment period and who do not continue in Part 2. A Safety Follow-up visit will be performed 10 weeks after their last study treatment administration (Week 106 +/-7 days).

[c] A diagnostic characterization form will be completed at screening, Week 96, and EOT/EOS for symptomatic participants only. It will also be completed for any pre-symptomatic participant who becomes symptomatic during the course of the study; for these participants, the diagnostic characterization form will be completed at the first visit in which they exhibit clinical symptomatology.

[d] The COAs consist of the Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center frontotemporal lobar degeneration Behavior and Language Domains (CDR® plus NACC FTLD), Frontotemporal Dementia Rating Scale (FRS), Clinical Global Impression-Improvement (CGI-I), Clinical Global Impression-Severity (CGI-S), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), European Quality of Life-5 Dimensions (EQ-5D), Zarit Burden Interview (ZBI), and the Resource Utilization in Dementia-Lite version (RUD-Lite). The CGI-I is not administered at baseline. The study participant COAs will be performed prior to study treatment administration (if applicable) and prior to any stressful procedures (eg, blood collections, lumbar puncture, imaging). At-risk participants (CDR® plus NACC FTLD-SB score ≤0.5) require the study partner at the COA visits only. At-risk participants who become symptomatic (CDR® plus NACC FTLD-SB score >0.5) during the study treatment period require the study partner at each visit moving forward through the Part1/Part 2 EOS or Safety Follow-up visit, whichever is later.

[e] All AEs and serious AEs (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 treatment that occur at any time should 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 treatment administration (when applicable).

[f] A complete physical examination (PE) will be performed at screening, at Weeks 24, 48, 72, 96 and at EOT/EOS/Safety Follow-up (prior to study treatment administration). A symptom-directed examination is required at all other specified time points. For visits with study treatment administration, the PE should be performed prior to the infusion. The examination will be performed by a physician or by a nurse practitioner or physician's assistant under the supervision of a physician. Complete PEs will include 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 the opinion of the health care provider. Symptom-directed examinations should include cardiovascular, respiratory, and gastrointestinal systems, plus any other pertinent system as required. Height (cm) will be measured at screening. Record abnormalities observed at screening on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the AE eCRF.

[g] A complete neurological examination will be performed at screening, at Weeks 24, 48, 72, 96 and at EOT/EOS/Safety Follow-up (prior to study treatment administration). A symptom-directed examination is required at all other specified time points. For visits with study treatment administration, this should be

performed prior to the infusion. A complete neurologic examination should include the evaluation of consciousness, orientation, cranial nerves, motor and sensory system, coordination and gait, and reflexes. A 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 eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the AE eCRF.

[h] Vital signs will be recorded as per standard institutional practice. 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 (pre-dose only) at the same visits that vital signs are taken.

[i] Samples will be collected prior to study treatment administration (if applicable).

[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] Triplicate 12-lead ECGs will be obtained after the participant has been in the supine position for at least 5 minutes. Additional ECG monitoring must be performed during the treatment period, if clinically indicated. On specified dosing days, the ECG will be obtained prior to study treatment administration and within 60 minutes after the end of infusion.

[l] Magnetic resonance imaging scans of the brain will be performed and centrally reviewed for assessment of safety and for evaluation of global and regional brain volumes, volume of white matter hyperintensities (measured by volumetric MRI); brain perfusion (measured by arterial spin labeling MRI); and fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity (measured by diffusion-tensor imaging). During study treatment, MRI is to be performed within ±7 days of a treatment visit and prior to study treatment administration (if applicable). If an MRI and an LP are performed in the same visit, either (a) the MRI should be performed first or (b) the MRI should be performed at least 3 days after the LP. This minimizes the effect of CSF removal on brain volume measurements.

[m] **Optional** CSF samples will be collected via lumbar puncture prior to study treatment administration (if applicable). Any treated participant who has consented to the optional lumbar puncture assessment and discontinues prematurely should have CSF drawn, unless CSF has been drawn within 12 weeks of discontinuation.

[n] The coagulation panel will only be assessed at the Week 92 visit **only** for participants who have consented to optional CSF sampling.

[o] Details on timing of PK serum samples, ADA serum samples, PGRN plasma samples, serum NfL samples, exploratory biomarker plasma samples, and exploratory biomarker whole blood samples are provided in Table 5.

[p] Blood serum samples will be collected for determination of ADA. In the event of an infusion reaction, a sample of blood should be obtained for PK serum and ADA assessment of AL001 or placebo, and testing should be performed for c-reactive protein, tryptase, and interleukin 6.

[q] If the assessment is unable to be performed at the scheduled visit, the assessments may be performed remotely or at a future on-site visit with approval from the Medical Monitor. Refer to Section 6.4 for additional details on trial adaptations when on-site visits cannot be performed, or when a participant is nonverbal.

[r] Winterlight Labs Speech Assessments (WLA) (for participants and study partners who are proficient in English, Spanish, French, Dutch, or German and who agree to participate in the optional assessments only) will be conducted at home. Assessments are conducted at home within 7 days prior to study treatment administration 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.

[s] A Part 1 EOT visit will be completed by participants who discontinue study treatment 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.

[t] A Part 1 EOS visit will be completed by participants who discontinue study treatment and all assessments. Part 1 EOS assessments should be completed as soon as possible after the decision is made. Study treatment administration will only occur at the Part 1 EOS visit (at the scheduled Week 96 visit) for participants who complete the Part 1 96-week treatment period and who do not continue in Part 2.

[u] If the participant cannot complete the Sheehan-STS evaluation, a clinical evaluation of suicide risk should be completed by a medically qualified staff member. The completion and outcome of this assessment should be recorded in the eCRF and documented in the participant's source documents.

Note: Unscheduled visits may occur at any time while the participant is enrolled in the study. Assessments should be performed as clinically indicated.

Table 5: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Sample Assessments - Part 1 Treatment Period

Participants	Time Point	PK Serum Sample[a]	ADA Serum Sample	PGRN Plasma Sample	NfL Serum Sample	Exploratory Biomarker Plasma Sample[b]	Exploratory Biomarker Whole Blood Sample[b]
All participants	Screening				x		
	V1 (Week 0): Pre-dose	x	x	x	x	x	x
	V1 (Week 0): End of infusion	x					
	V2 (Week 4): Pre-dose						
	V2 (Week 4): End of infusion						
	V3 (Week 8): Pre-dose	x		x	x	x	x
	V3 (Week 8): End of infusion	x					
	V4 (Week 12): Pre-dose	x	x	x			
	V4 (Week 12): End of infusion	x					
	V5 (Week 16): Pre-dose	x		x	x	x	x
	V5 (Week 16): End of infusion	x					
	V6 (Week 20): Pre-dose						
	V6 (Week 20): End of infusion						
	V7 (Week 24): Pre-dose	x	x	x	x	x	x
	V7 (Week 24): End of infusion	x					
	V8 (Week 28): Pre-dose						
	V8 (Week 28): End of infusion						
	V9 (Week 32): Pre-dose	x		x	x	x	x
	V9 (Week 32): End of infusion	x					
	V10 (Week 36): Pre-dose						
	V10 (Week 36): End of infusion						
	V11 (Week 40): Pre-dose	x		x	x	x	x
	V11 (Week 40): End of infusion	x					
	V12 (Week 44): Pre-dose						
	V12 (Week 44): End of infusion						
	V13 (Week 48): Pre-dose	x	x	x	x	x	x
	V13 (Week 48): End of infusion	x					

Table 5: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Sample Assessments - Part 1 Treatment Period (Continued)

Participants	Time Point	PK Serum Sample[a]	ADA Serum Sample	PGRN Plasma Sample	NfL Serum Sample	Exploratory Biomarker Plasma Sample[b]	Exploratory Biomarker Whole Blood Sample[b]
	V14 (Week 52): Pre-dose						
	V14 (Week 52): End of Infusion						
	V15 (Week 56): Pre-dose						
	V15 (Week 56): End of Infusion						
	V16 (Week 60): Pre-dose						
	V16 (Week 60): End of Infusion						
	V17 (Week 64): Pre-dose						
	V17 (Week 64): End of Infusion						
	V18 (Week 68): Pre-dose						
	V18 (Week 68): End of Infusion						
	V19 (Week 72): Pre-dose	x	x	x	x	x	x
	V19 (Week 72): End of Infusion	x					
	V20 (Week 76): Pre-dose						
	V20 (Week 76): End of Infusion						
	V21 (Week 80): Pre-dose						
	V21 (Week 80): End of Infusion						
	V22 (Week 84): Pre-dose						
	V22 (Week 84): End of Infusion						
	V23 (Week 88): Pre-dose						
	V23 (Week 88): End of Infusion						
	V24 (Week 92): Pre-dose						
	V24 (Week 92): End of Infusion						
	V25 (Week 96): Pre-dose	x	x	x	x	x	x
	V25 (Week 96): End of Infusion	x					
	Safety Follow-up	x	x	x			
	Part 1 EOT/EOS	x	x	x	x	x	x

ADA=antidrug antibody; ECG=electrocardiogram; EOS=End of Study; EOT=End of Treatment; PK=pharmacokinetic; V=visit.

[a] The window for PK serum samples is within 15 minutes after the end of the infusion. Note that the end of the infusion time includes the time required for intravenous flushing.

[b] [redacted]

Note: Unscheduled visits may occur at any time while the participant is enrolled in the study. Assessments should be performed as clinically indicated.

Table 6: Schedule of Assessments (Part 2 Optional OLE: Through Week 144)

Procedures[p]	Treatment Period											
Visits	**V26[a]**	**V27**	**V28**	**V29**	**V30**	**V31**	**V32**	**V33**	**V34**	**V35**	**V36**	**V37**
Study week	**100**	**104**	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**
Visit window (days)		**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Informed consent	x[a]											
Diagnostic characterization[b]												
COAs[c]						x						x
Review of AEs and concomitant medications[d]	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination[e]	x	x	x	x	x	x[e]	x	x	x	x	x	x[e]
Neurological examination[f]	x	x	x	x	x	x[f]	x	x	x	x	x	x[f]
Vital signs and weight[g]	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy test[h,i]	x	x	x	x	x	x	x	x	x	x	x	x
Sheehan-STS[r]	x	x	x	x	x	x	x	x	x	x	x	x
ECG[j]						x						x
Brain MRI[k]												x
Optional lumbar puncture/CSF[l]												x
Chemistry and hematology[h]	x			x		x			x			x
Coagulation[h,m]											x	
Urinalysis[h]						x						x
ADA serum samples[h,n,o]	x			x		x						x
PGRN plasma samples[h,n]	x			x		x			x			x
NfL serum samples[h,n]	x			x		x			x			x
Exploratory biomarker plasma samples[h,n]	x			x		x			x			x
Exploratory biomarker whole blood samples[h,n]	x			x		x			x			x
PK serum samples[h,n,o]	x			x		x			x			x
Winterlight Labs Speech Assessment (Optional)[q]	x	x	x	x	x	x	x	x	x	x	x	x
Study treatment administration	x	x	x	x	x	x	x	x	x	x	x	x

ADA=antidrug antibody; AE=adverse event; COA=clinical outcome assessment; CSF=cerebrospinal fluid; ECG=electrocardiogram; LP=lumbar puncture; MRI=magnetic resonance imaging; NfL=neurofilament light chain; PGRN=progranulin protein; 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 96), 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 100 study treatment administration), will complete the Week 96 visit and continue to Part 2 (Week 100) to receive their next regularly scheduled dose of AL001 according to the OLE administration schedule (continuation from Week 96 to Week 100). Visit 26/Week 100 of Part 2 (Optional OLE) will be conducted 4 weeks after Visit 25/Week 96 of the Part 1 Treatment Period for those participants who are eligible to participate.

[b] A diagnostic characterization form will be completed for symptomatic participants at Week 196/Part 2 EOS. It will also be completed for any at-risk participant who becomes symptomatic during the course of the study; for these participants, the diagnostic characterization form will be completed at the first visit in which they exhibit clinical symptomatology.

[c] The COAs consist of the Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center frontotemporal lobar degeneration Behavior and Language Domains (CDR® plus NACC FTLD), Frontotemporal Dementia Rating Scale (FRS), Clinical Global Impression-Improvement (CGI-I), Clinical Global Impression-Severity (CGI-S), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), European Quality of Life-5 Dimensions (EQ-5D), Zarit Burden Interview (ZBI), and the Resource Utilization in Dementia-Lite version (RUD-Lite). The CGI-I will not be administered at baseline. The study participant COAs will be performed prior to study treatment administration (if applicable) and prior to any stressful procedures (eg, blood collections, lumbar puncture, imaging). At-risk participants (CDR® plus NACC FTLD-SB score ≤0.5) require the study partner at the COA visits only. At-risk participants who become symptomatic (CDR® plus NACC FTLD-SB score >0.5) during the study treatment period require the study partner at each visit moving forward through the Part1/Part 2 EOS or Safety Follow-up visit, whichever is later.

[d] All AEs and serious AEs (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 treatment that occur at any time should 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 treatment administration (when applicable).

[e] A complete physical examination (PE) will be performed at Week 120, Week 144, Week 168, Week 196 and at EOS/Safety Follow-up (prior to study treatment administration). A symptom-directed examination is required at all other specified time points. For visits with study treatment administration, the PE should be performed prior to the infusion. The examination will be performed by a physician or by a nurse practitioner or physician's assistant under the supervision of a physician. Complete PEs will include 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 the opinion of the health care provider. Symptom-directed examinations should include cardiovascular, respiratory, and gastrointestinal systems, plus any other pertinent system as required. Height (cm) will be measured at screening. Record abnormalities observed at screening on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the AE eCRF.

[f] A complete neurological examination will be performed at Week 120, Week 144, Week 168, Week 196 and at EOT/EOS/Safety Follow-up (prior to study treatment administration). A symptom-directed examination is required at all other specified time points. For visits with study treatment administration, this should be performed prior to the infusion. A complete neurologic examination should include the evaluation of consciousness, orientation, cranial nerves, motor and sensory system, coordination and gait, and reflexes. A 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 eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the AE eCRF.

[g] Vital signs will be recorded as per standard institutional practice. 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 (pre-dose only) at the same visits that vital signs are taken.

[h] Samples will be collected prior to study treatment administration (if applicable).

[i] 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.

[j] Triplicate 12-lead ECGs will be obtained after the participant has been in the supine position for at least 5 minutes. Additional ECG monitoring must be performed during the treatment period, if clinically indicated. On specified dosing days, the ECG will be obtained prior to study treatment administration and within 60 minutes after the end of infusion.

[k] Magnetic resonance imaging scans of the brain will be performed and centrally reviewed for assessment of safety and for evaluation of global and regional brain volumes, volume of white matter hyperintensities (measured by volumetric MRI); brain perfusion (measured by arterial spin labeling MRI); and fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity (measured by diffusion-tensor imaging). During study treatment, MRI is to be performed within ±7 days of a treatment visit and prior to study treatment administration (if applicable). If an MRI and an LP are performed in the same visit, either (a) the MRI should be performed first or (b) the MRI should be performed at least 3 days after the LP. This minimizes the effect of CSF removal on brain volume measurements.

[l] **Optional** CSF samples will be collected via lumbar puncture prior to study treatment administration (if applicable). Any treated participant who has consented to the optional lumbar puncture assessment and discontinues prematurely should have CSF drawn, unless CSF has been drawn within 12 weeks of discontinuation.

[m] The coagulation panel will only be assessed at the Week 140 visit **only** for participants who have consented to optional CSF sampling.

[n] Details on timing of PK serum samples, ADA serum samples, PGRN plasma samples, serum NfL samples, exploratory biomarker plasma samples, and exploratory biomarker whole blood samples are provided in Table 8.

[o] Blood serum samples will be collected for determination of ADA. In the event of an infusion reaction, a sample of blood should be obtained for PK serum and ADA assessment of AL001 or placebo, and testing should be performed for c-reactive protein, tryptase, and interleukin 6.

[p] If the assessment is unable to be performed at the scheduled visit, the assessments may be performed remotely or at a future on-site visit with approval from the Medical Monitor. Refer to Section 6.4 for additional details on trial adaptations when on-site visits cannot be performed, or when a participant is nonverbal.

[q] Winterlight Labs Speech Assessments (WLA) (for participants and study partners who are proficient in English, Spanish, French, Dutch, or German and who agree to participate in the optional assessments only) will be conducted at home. Assessments are conducted at home within 7 days prior to study treatment administration 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] If the participant cannot complete the Sheehan-STS evaluation, a clinical evaluation of suicide risk should be completed by a medically qualified staff member. The completion and outcome of this assessment should be recorded in the eCRF and documented in the participant's source documents.

Note: Unscheduled visits may occur at any time while the participant is enrolled in the study. Assessments should be performed as clinically indicated.

Table 7: Schedule of Assessments (Part 2 Optional OLE: Through Week 196)

Procedures[q]	Treatment Period													Part 2 EOS[b,s]	Safety Follow-up[a]
Visits	**V38**	**V39**	**V40**	**V41**	**V42**	**V43**	**V44**	**V45**	**V46**	**V47**	**V48**	**V49**	**V50[s]**		
Study week	**148**	**152**	**156**	**160**	**164**	**168**	**172**	**176**	**180**	**184**	**188**	**192**	**196**		
Visit window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Diagnostic characterization[c]													x	x	
COAs[d]						x							x	x	
Review of AEs and concomitant medications[e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination[f]						x[f]							x[f]	x[f]	x[f]
Neurological examination[g]						x[g]							x[g]	x[g]	x[g]
Vital signs and weight[h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy test[i,j]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Sheehan-STS[t]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG[k]						x							x	x	x
Brain MRI[l]													x	x	
Optional lumbar puncture/CSF[m]													x	x	
Chemistry and hematology[i]						x							x	x	x
Coagulation[i,n]												x			
Urinalysis[i]						x							x	x	x
ADA serum samples[i,o,p]						x							x	x	x
PGRN plasma samples[i,o]						x							x	x	x
NfL serum samples[i,o]						x							x	x	
Exploratory biomarker plasma samples[i,o]						x							x	x	
Exploratory biomarker whole blood samples[i,o]						x							x	x	
PK serum samples[i,o,p]						x							x	x	x
Winterlight Labs Speech Assessment (Optional)[r]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Study treatment administration	x	x	x	x	x	x	x	x	x	x	x	x	x	x[b]	

ADA=antidrug antibody; AE=adverse event; COA=clinical outcome assessment; CSF=cerebrospinal fluid; ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; LP=lumbar puncture; MRI=magnetic resonance imaging; NfL=neurofilament light chain; PGRN=progranulin protein; PK=pharmacokinetic; Sheehan-STS=Sheehan-Suicidality Tracking Scale; V=visit.

[a] A Safety Follow-up visit will be performed 10 weeks following the last dose of AL001.

[b] Participants who discontinue study treatment and/or all assessments prior to completing the Part 2 96-week OLE period will complete a Part 2 EOS visit as soon as possible after the decision is made. Study treatment administration will only occur at the Part 2 EOS visit (at the scheduled Week 196 time point) for participants who complete the Part 2 96-week OLE period.

[c] A diagnostic characterization form will be completed for symptomatic participants at Week 196/Part 2 EOS. It will also be completed for any at-risk participant who becomes symptomatic during the course of the study; for these participants, the diagnostic characterization form will be completed at the first visit in which they exhibit clinical symptomatology.

[d] The COAs consist of the Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center frontotemporal lobar degeneration Behavior and Language Domains (CDR® plus NACC FTLD), Frontotemporal Dementia Rating Scale (FRS), Clinical Global Impression-Improvement (CGI-I), Clinical Global Impression-Severity (CGI-S), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), European Quality of Life-5 Dimensions (EQ-5D), Zarit Burden Interview (ZBI), and the Resource Utilization in Dementia-Lite version (RUD-Lite). The CGI-I is not administered at baseline. The study participant COAs will be performed prior to study treatment administration (if applicable) and prior to any stressful procedures (eg, blood collections, lumbar puncture, imaging). At-risk participants (CDR® plus NACC FTLD-SB score ≤0.5) require the study partner at the COA visits only. At-risk participants who become symptomatic (CDR® plus NACC FTLD-SB score >0.5) during the study treatment period require the study partner at each visit moving forward through the Part1/Part 2 EOS or Safety Follow-up visit, whichever is later.

[e] All AEs and serious AEs (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 treatment that occur at any time should 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 treatment administration (when applicable).

[f] A complete physical examination (PE) will be performed at Week 120, Week 144, Week 168, Week 196 and at EOS/Safety Follow-up (prior to study treatment administration). A symptom-directed examination is required at all other specified time points. For visits with study treatment administration, the PE should be performed prior to the infusion. The examination will be performed by a physician or by a nurse practitioner or physician's assistant under the supervision of a physician. Complete PEs will include 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 the opinion of the health care provider. Symptom-directed examinations should include cardiovascular, respiratory, and gastrointestinal systems, plus any other pertinent system as required. Height (cm) will be measured at screening. Record abnormalities observed at screening on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the AE eCRF.

[g] A complete neurological examination will be performed at Week 120, Week 144, Week 168, Week 196 and at EOS/Safety Follow-up (prior to study treatment administration). A symptom-directed examination is required at all other specified time points. For visits with study treatment administration, this should be performed prior to the infusion. A complete neurologic examination should include the evaluation of consciousness, orientation, cranial nerves, motor and sensory system, coordination and gait, and reflexes. A 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 eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the AE eCRF.

[h] Vital signs will be recorded as per standard institutional practice. On dosing days, vital signs will be recorded prior to infusion (pre-dose), within 15 minutes after the end of infusion, and once at all other specified time points as indicated. Weight (kg) will be collected (pre-dose only) at the same visits that vital signs are taken.

[i] Samples will be collected prior to study treatment administration (if applicable).

[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] Triplicate 12-lead ECGs will be obtained after the participant has been in the supine position for at least 5 minutes. Additional ECG monitoring must be performed during the treatment period, if clinically indicated. On specified dosing days, the ECG will be obtained prior to study treatment administration and within 60 minutes after the end of infusion.

[l] Magnetic resonance imaging scans of the brain will be performed and centrally reviewed for assessment of safety and for evaluation of global and regional brain volumes, volume of white matter hyperintensities (measured by volumetric MRI); brain perfusion (measured by arterial spin labeling MRI); and fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity (measured by diffusion-tensor imaging). During study treatment, MRI is to be performed within ±7 days of a treatment visit and prior to study treatment administration (if applicable). If an MRI and an LP are performed in the same visit, either (a) the MRI should be performed first or (b) the MRI should be performed at least 3 days after the LP. This minimizes the effect of CSF removal on brain volume measurements.

[m] **Optional** CSF samples will be collected via lumbar puncture prior to study treatment administration (if applicable). Any treated participant who has consented to the optional lumbar puncture assessment and discontinues prematurely should have CSF drawn, unless CSF has been drawn within 12 weeks of discontinuation.

[n] The coagulation panel will only be assessed at the Week 192 visit **only** for participants who have consented to optional CSF sampling.

[o] Details on timing of PK serum samples, ADA serum samples, PGRN plasma samples, serum NfL samples, exploratory biomarker plasma samples, and exploratory biomarker whole blood samples are provided in Table 8.

[p] Blood serum samples will be collected for determination of ADA. In the event of an infusion reaction, a sample of blood should be obtained for PK serum and ADA assessment of AL001 or placebo, and testing should be performed for c-reactive protein, tryptase, and interleukin 6.

[q] If the assessment is unable to be performed at the scheduled visit, the assessments may be performed remotely or at a future on-site visit with approval from the Medical Monitor. Refer to Section 6.4 for additional details on trial adaptations when on-site visits cannot be performed, or when a participant is nonverbal.

[r] Winterlight Labs Speech Assessments (WLA) (for participants and study partners who are proficient in English, Spanish, French, Dutch, or German and who agree to participate in the optional assessments only) will be conducted at home. Assessments are conducted at home within 7 days prior to study treatment administration 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.

[s] At Week 196, participants who complete the Part 2 96-week OLE period will complete a Part 2 EOS visit at the scheduled Week 196 time point. Study treatment administration will only occur at the Part 2 EOS visit (at the scheduled Week 196 time point) for participants who complete the Part 2 96-week OLE period. Participants who complete Visit 50/Week 196 will return for a Safety Follow-up visit 10 weeks after their last AL001 administration (Week 206, +/-7 days).

[t] If the participant cannot complete the Sheehan-STS evaluation, a clinical evaluation of suicide risk should be completed by a medically qualified staff member. The completion and outcome of this assessment should be recorded in the eCRF and documented in the participant's source documents.

Note: Unscheduled visits may occur at any time while the participant is enrolled in the study. Assessments should be performed as clinically indicated.

Table 8: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Sample and Imaging Assessments - Part 2 (Optional OLE)

Time Point	Serum PK Sample [a]	Serum ADA Sample	PGRN Plasma Sample	NfL Serum Sample	Exploratory Biomarker Plasma Sample[b]	Exploratory Biomarker Whole Blood Sample[b]
V26 (Week 100): Pre-dose	x	x	x	x	x	x
V26 (Week 100): End of Infusion	x					
V29 (Week 112): Pre-dose	x	x	x	x	x	x
V29 (Week 112): End of infusion	x					
V31 (Week 120): Pre-dose	x	x	x	x	x	x
V31 (Week 120): End of infusion	x					
V34 (Week 132): Pre-dose	x		x	x	x	x
V34 (Week 132): End of infusion	x					
V37 (Week 144): Pre-dose	x	x	x	x	x	x
V37 (Week 144): End of infusion	x					
V43 (Week 168): Pre-dose	x	x	x	x	x	x
V43 (Week 168): End of infusion	x					
V50 (Week 196): Pre-dose	x	x	x	x	x	x
V50 (Week 196): End of infusion	x					
Safety Follow-up	x	x	x			
Part 2: EOS	x	x	x	x	x	x

ADA=antidrug antibody; ECG=electrocardiogram; EOS=End of Study; EOT=End of Treatment; PK=pharmacokinetic; V=visit.

[a] The window for PK serum samples is within 15 minutes after the end of the infusion. Note that the end of the infusion time includes the time required for intravenous flushing.

[b] [redacted]

Note: Unscheduled visits may occur at any time while the participant is enrolled in the study. Assessments should be performed as clinically indicated.

14.2. Appendix: Clinical Outcome Assessments

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 is the CDR® plus the Behavior and Language Domains from the NACC FTLD module. In this protocol, the global CDR® plus NACC FTLD score is used for the characterization of the cohorts (0, 0.5, 1, 2), and the CDR® plus NACC FTLD-SB is used as the primary efficacy endpoint.

Clinical Dementia Rating Scale (CDR®):

Washington University's CDR® is a global assessment instrument that yields global scores. The sum of boxes score is a detailed quantitative general index that provides more information than the CDR®-GS in participants with mild dementia (O'Bryant 2010). The CDR® characterizes 6 domains of cognitive and functional performance applicable to Alzheimer's disease and related dementias: Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. The necessary information to make each rating is obtained through a semi-structured interview of the participant and a reliable informant or collateral source (eg, a caregiver).

Clinical Global Impression-Severity (CGI-S):

The CGI-S is a 7-point Likert scale that is used by a clinician to rate the severity of a participant's disease relative to the clinician's past experience with patients who have the same diagnosis.

Clinical Global Impression-Improvement (CGI-I):

The CGI-I is a 7-point Likert scale that is used by a clinician to rate how much a participant's disease has improved or worsened relative to baseline. The CGI-I will be administered in this study to assess (a) total improvement/worsening; (b) total improvement/worsening of behavior, motivation, and social cognition symptoms; and (c) total improvement/worsening of language abilities.

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

The RBANS is a collection of 12 subtests representing 5 neurocognitive domains: Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory. The raw scores from each subtest within a domain are converted to a summary score, or Index Score, for the domain by consulting normative data tables. The RBANS also provides an overall Index Score that summarizes the patient's overall level of performance on this measure.

Frontotemporal Dementia Rating Scale (FRS):

The FRS is a 30-item scale designed to assess the frequency of problematic behaviors and difficulties with activities of daily living such as shopping, chores, telephone use, management of finances and medications, meal preparation and eating, self-care, and mobility.

European Quality of Life-5 Dimensions (EQ-5D):

The EQ-5D is a standardized instrument developed by the EuroQol Group and consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale. The EQ-5D descriptive system is comprised of 5 dimensions: Mobility, Self-care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. In the EQ visual analogue scale, the study partner (the proxy) is asked to rate the participant's health related quality of life in their (the proxy's) opinion on a vertical visual analogue scale, which can be used as a quantitative measure of the participant's health outcome. The EQ-5D is available in more than 170 languages and is available at https://euroqol.org/eq-5d-instruments/.

Zarit Burden Interview (ZBI):

The ZBI is a 29-item questionnaire (22 items in the revised questionnaire) that the participant's study partner completes using a 5-point scale (0, never; 4, near always) to determine the degree of burden that the participant's care places on the study partner. A sample ZBI can be found at http://dementiapathways.ie/_filecache/edd/c3c/89-zarit_burden_interview.pdf.

Resource Utilization in Dementia-Lite Version (RUD-Lite):

The RUD is a standardized instrument to compare economic costs and resource utilization in dementia across different countries. The RUD measures study partner's time, including informal care time. The RUD is available in 58 languages and is available as the full version (RUD) or an abbreviated version (RUD-Lite) (http://rudinstrument.com/).

Sheehan-Suicidality Tracking Scale (Sheehan-STS):

The Sheehan-STS is a brief scale designed to assess and monitor over time the core phenomena of suicidality. The Sheehan-STS is a sensitive psychometric tool to prospectively assess for treatment-emergent suicidal thoughts and behaviors. 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.

Optional Winterlight Labs Speech Assessments (WLA)

The optional Winterlight Lab Speech Assessments (WLA) are for participants and study partners who are proficient English, Spanish, French, Dutch, or German and who agree and are eligible to participate in these optional assessments.

If the participant and study partner are eligible, agree to, and provide consent for this optional assessment, WLA procedures will be performed at home, as detailed in the Schedules of Assessments (Table 3, Table 4, Table 6, and Table 7).

Winterlight Labs Speech Assessment (WLA) Overview

The WLA was developed to evaluate speech, language, and cognition using short samples of speech. Winterlight's software decomposes a speech sample into over 500 individual markers. These markers quantify both the acoustic and linguistic properties of the speech. Acoustic markers describe properties of the sound wave itself such as tone, speaking rate, pausing (both filled and unfilled), pitch, and spectral power. Linguistic markers are extracted from the content of speech (eg, transcripts) and include the frequency of different parts of speech (such as nouns,

verbs, pronouns, and prepositions) as well as more global measures of discourse coherence and the complexity of syntax and grammar.

To standardize the content of each speech sample and ensure that sufficient speech is collected, the WLA records participants' responses to a series of standard speech and language tasks. To allow for a greater range of free speech collection, the WLA also includes open-ended questions and journaling in place of structured neuropsychological tasks. While these tasks provide consistent subject matter, they also provide their own task-specific indices of performance. The WLA leverages both these task-specific outcomes as well as task-independent markers to evaluate an individual's cognitive performance.

The WLA is administered using an application on a tablet device that presents assessment questions and records audio of the participant. It is composed of various established aspects from paper/interview-based assessments, including picture description, story recall, and object recognition as well as open-ended questions and journaling.

These assessments are conducted at home within days prior to study treatment administration. Assessments will be supervised by the study partner.

Document Approvals

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