CLINICAL STUDY PROTOCOL

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

Investigational Product:	AL001, human recombinant anti-human Sortilin IgG1 monoclonal antibody
Indication:	Frontotemporal Dementia (FTD)
Study Phase:	2
IND Number:	135892
EudraCT Number:	2019-000138-20
ClinicalTrials.gov Identifier:	NCT03987295
Sponsor:	Alector, Inc. 131 Oyster Point Boulevard, Suite 600 South San Francisco, CA 94080, US Telephone: +1 650-837-0384
Sponsor Medical Monitor:	Sam Jackson, MD [redacted]
Version of Protocol:	Version 4.0
Date of Protocol:	04 Feb 2021
Previous Versions:	Version 3.2 United Kingdom (23 Nov 2020) Version 3.1 (13 Jul 2020) Version 3.0 (02 Jun 2020) Version 2.0 (26 Sep 2019) Version 1.4 (12 Sep 2019) Version 1.3 (02 Aug 2019) Version 1.2 (24 Jun 2019) Version 1.1 (22 Apr 2019) Version 1.0 (09 Apr 2019) Original Protocol

SPONSOR SIGNATURE PAGE

Study Title:	A Phase 2, Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AL001 in Heterozygous Carriers of *Granulin* or *C9orf72* Mutations Causative of Frontotemporal Dementia
Version No.	Version 4.0
Protocol Date:	04 Feb 2021

Protocol accepted and approved by:

Alector Medical Lead
Sam Jackson, MD
Alector, Inc.
131 Oyster Point Boulevard, Suite 600
South San Francisco, CA 94080, US

[redacted] 4 Feb 2021

Signature Date

PROTOCOL APPROVAL – LEAD STATISTICIAN

Study Title:	A Phase 2, Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AL001 in Heterozygous Carriers of *Granulin* or *C9orf72* Mutations Causative of Frontotemporal Dementia
Version No.	Version 4.0
Protocol Date:	04 Feb 2021

Protocol accepted and approved by:

Lead Statistician
YiJie, Liao PhD
Alector, Inc.
131 Oyster Point Boulevard, Suite 600
South San Francisco, CA 94080, US

[redacted] 04Feb2021

Signature Date

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Phase 2, Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AL001 in Heterozygous Carriers of *Granulin* or *C9orf72* Mutations Causative of Frontotemporal Dementia" and the accompanying Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the protocol, Version 4.0, dated 04 Feb 2021, the International Council on Harmonisation Tripartite Guideline E6(R2): Good Clinical Practice and all applicable government regulations. I agree to administer study drug only to participants under my personal supervision or the supervision of a sub-investigator.

I will not supply the study drug 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.

Signature of Investigator	Date
Printed Name of Investigator	Site Number

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PROTOCOL SYNOPSIS

Protocol Number:	AL001-2
Title:	A Phase 2, Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AL001 in Heterozygous Carriers of *Granulin* or *C9orf72* Mutations Causative of Frontotemporal Dementia
Sponsor:	Alector, Inc. 131 Oyster Point Boulevard, Suite 600 South San Francisco, CA 94080, US
Study Phase:	Phase 2
Investigational Sites:	Approximately 13 investigational sites in North America and Europe
Indication:	Frontotemporal dementia (FTD)
Study Design:	The study has two parts: A phase 2 open-label treatment period (Part 1), followed by an open-label extension (OLE) period (Part 2). Part 1 is a 96-week evaluation of the safety, tolerability, pharmacokinetic (PK), pharmacodynamic (PD), and clinical effect of AL001 administered intravenously (60 mg/kg, every 4 weeks [q4w]), for a total of 25 doses (96-week dosing period), in asymptomatic and symptomatic carriers of loss-of-function *GRN* mutations causative of FTD, and in symptomatic carriers of *C9orf72* hexanucleotide repeat expansion mutations causative of FTD. Part 2 is an optional OLE for eligible participants who have completed the 96-week Part 1 treatment period. The OLE period will evaluate the long-term safety and tolerability of AL001 administered at the same dose and regimen as Part 1 (60 mg/kg, q4w), for up to a total of 25 doses (96-week optional OLE period). **Part 1 (Treatment Period):** In Part 1 of the study, two cohorts will be enrolled: a *GRN* Cohort and a *C9orf72* Cohort. Both cohorts will enroll symptomatic participants with FTD; in addition, asymptomatic participants may enroll into the *GRN* Cohort, but only if they participated in the Phase 1 AL001-1 study. Both asymptomatic and symptomatic carriers of a *GRN* mutation who participated in Study AL001-1 may enroll into the *GRN* Cohort if they completed dosing, the required follow-up portion of Study AL001-1, did not experience AEs that would indicate that continued dosing with AL001 would be unsafe, and meet the inclusion/exclusion criteria of Part 1 of Study AL001-2. In addition, new participants who are symptomatic carriers of a *GRN* mutation will also be enrolled into the *GRN* Cohort. Symptomatic FTD participants may enroll in Part 1 of the study if they have either 1 or more of the 6 behavioral/cognitive symptoms required for a diagnosis of possible behavioral variant FTD (bv FTD) (Rascovsky 2011), or a diagnosis of primary progressive aphasia (PPA) (Gorno-Tempini 2011). New symptomatic participants must also have a Clinical Dementia Rating (CDR®) plus NACC frontotemporal lobar degeneration (FTLD) global score of 0.5, 1, or 2. In Part 1, all participants will be administered open-label, IV AL001 at the investigational site (60 mg/kg, q4w) for 25 doses over a 96-week dosing period. An independent Data Monitoring Committee (iDMC) will review safety data during the course of Part 1 of the study to provide recommendations to Alector on study conduct. The iDMC will be comprised of two physicians (including one with disease

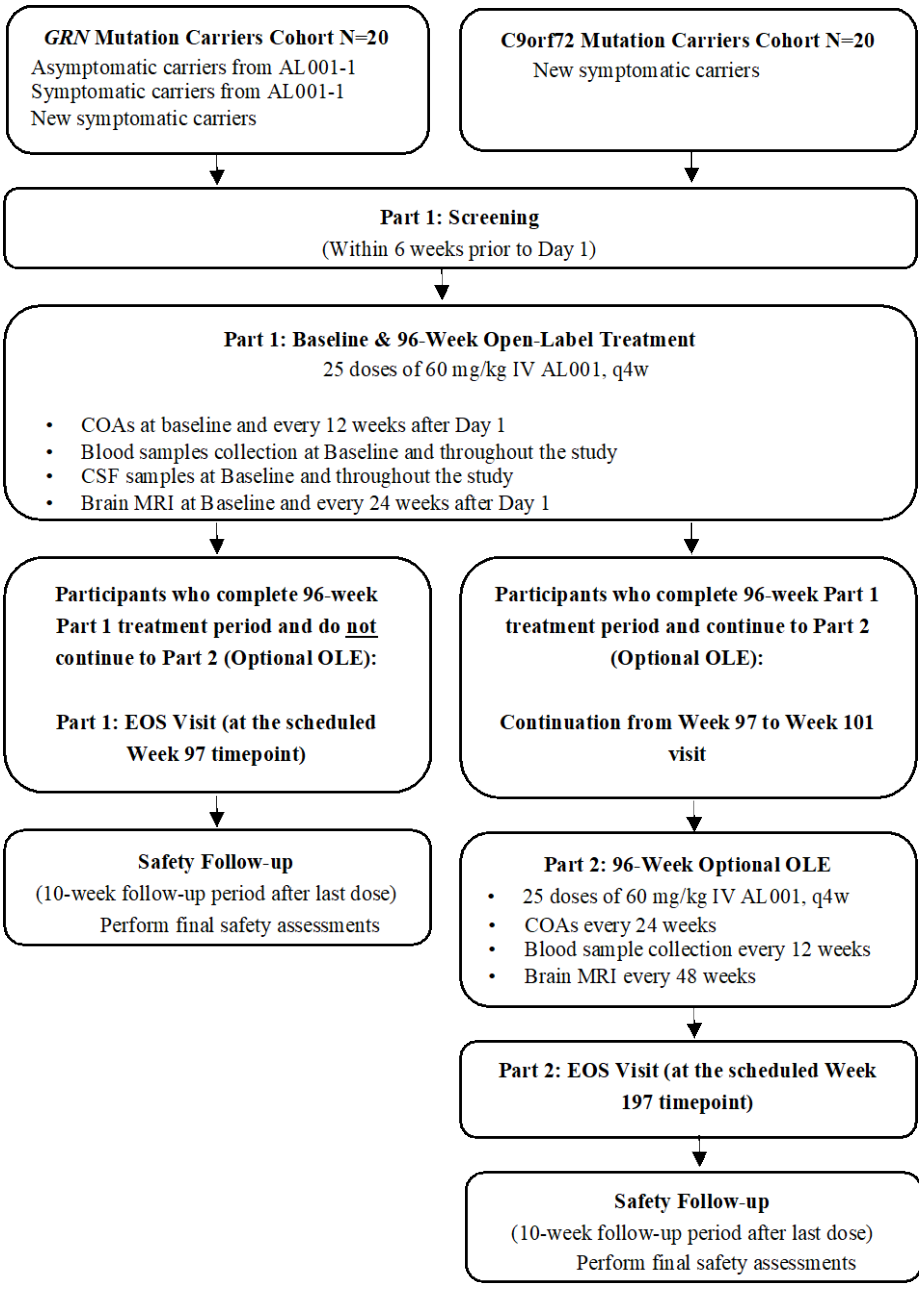
	area expertise) and a statistician, each of whom are independent from Alector. Data reviews will be conducted after the first 6 participants complete approximately 12 weeks of study drug, and then every 6 months thereafter until the last participant completes Part 1 of the study. The details of the iDMC are provided in a separate charter. The primary objective of Part 1 of the study is to assess safety and tolerability of 96-week q4w dosing of IV AL001. Secondary and exploratory objectives of Part 1 include evaluating the PK and the preliminary effect of AL001 on PD biomarkers and COAs in asymptomatic and symptomatic participants. For PD biomarkers evaluation, the aims are to evaluate increases in PGRN levels after repeated IV dosing of AL001 in the blood plasma and CSF of asymptomatic and symptomatic participants, to evaluate changes in PD fluid biomarkers of neurodegeneration, lysosomal function, and glial activity, and to evaluate changes in imaging PD measures. **Part 2 (Optional Open-Label Extension):** Part 2 of the study is an optional 96-week, OLE period to assess the long-term safety and tolerability of AL001 in participants who have completed 96 weeks of treatment on Part 1 of the study. 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. Continued study treatment in the optional OLE will be IV AL001 60 mg/kg, q4w (i.e., same dose and treatment regimen as in Part 1). An individual participant may continue to receive AL001 in the OLE portion of the study for up to 25 doses over a 96-week dosing period, or until AL001 is commercially available in the country where the participant is being treated, whichever is earlier. In the event that an individual's participation in the OLE will extend beyond 96 weeks because AL001 is not commercially available in their country, they may be eligible to continue to receive AL001 under another Alector protocol or program. Participants will be discontinued from the OLE in the event of long-term placement in a skilled nursing facility; a CDR® plus NACC FTLD global score >2; if, in the opinion of the investigator and Alector, they are unable to follow protocol procedures; or, if they develop intercurrent illness that would confound the interpretation of safety and/or efficacy data.
Objectives, Part 1 (Treatment Period):	**Primary Objective – Part 1 (Treatment Period)** The primary objective of the treatment period of the study is to evaluate the safety and tolerability of intravenous (IV) administration of AL001 over 96 weeks in asymptomatic and symptomatic carriers of a *granulin* (*GRN*) mutation causative of frontotemporal dementia (FTD) and in symptomatic carriers of a *C9orf72* mutation causative of FTD. **Secondary Objectives– Part 1 (Treatment Period)** The secondary objectives of the treatment period of the study are to evaluate the effect of IV administration of AL001 over 96 weeks in asymptomatic and symptomatic carriers of a *GRN* mutation causative of FTD and in symptomatic carriers of a *C9orf72* mutation causative of FTD on the following: • Pharmacokinetics (PK) • Longitudinal plasma and cerebrospinal fluid (CSF) progranulin (PGRN) concentration levels

	• Longitudinal levels of Sortilin in white blood cells (WBCs) **Exploratory Objectives – Part 1 (Treatment Period)** The exploratory objectives of the treatment period of the study are to assess the effect of IV administration of AL001 over 96 weeks in asymptomatic and symptomatic carriers of a *GRN* mutation causative of FTD and in symptomatic carriers of a *C9orf72* mutation causative of FTD on the following: • Longitudinal blood, plasma, and CSF concentration levels of exploratory pharmacodynamic (PD) biomarkers of neurodegeneration, lysosomal function, and glial activity • Magnetic resonance imaging (MRI) measures to evaluate changes in the brain • Correlations among exploratory fluid PD biomarkers, imaging PD measures, and clinical outcome assessments (COAs) • Clinical progression as measured by COAs
Objectives, Part 2 (Optional Open-Label Extension):	**Primary Objective – Part 2 (Optional OLE)** The primary objective of the OLE period of the study is to assess the long-term safety and tolerability of IV administration of AL001 in participants who have completed 96 weeks of treatment on Part 1 of the study. **Exploratory Objectives – Part 2 (Optional OLE)** COAs, correlative assessments (e.g., biomarker) and other efficacy assessments conducted during the OLE are considered exploratory. The exploratory objectives of the OLE period of the study are to assess the long-term effect of IV administration of AL001 in participants who have completed 96 weeks of treatment on Part 1 of the study on the following: • Pharmacokinetics (PK) • Longitudinal plasma progranulin (PGRN) concentration levels • Longitudinal blood and plasma levels of exploratory pharmacodynamic (PD) biomarkers of neurodegeneration, lysosomal function, and glial activity • Magnetic resonance imaging (MRI) measures to evaluate changes in the brain • Correlations among exploratory fluid PD biomarkers, imaging PD measures, and clinical outcome assessments (COAs) • Clinical progression as measured by COAs

Number of Participants Planned:	**Part 1 (Treatment Period)**
	Approximately 40 male or female participants 18 to 85 years of age will be enrolled at approximately 13 investigational sites in North America and Europe.
	Two cohorts will be enrolled:
	• *GRN* mutation Cohort (up to 20 asymptomatic and symptomatic participants), including:
	  ○ All asymptomatic and symptomatic participants in Study AL001-1 may be enrolled
	  ○ New symptomatic *GRN* mutation carriers may be enrolled

	• *C9orf72* mutation Cohort (up to 20 new symptomatic participants) **Part 2 (Optional OLE)** Participants who complete Part 1 may be eligible for continued treatment with AL001.

Study Population:	**Part 1 (Treatment Period)**
	Prospective participant meets all of the following criteria specific to their applicable participant category:
	<u>*Participant Category 1: GRN* Mutation Carriers, Symptomatic, from Study AL001-1</u>
	• Completed Study AL001-1 through the Day 57 visit and did not experience adverse events (AEs) that the investigator deems would prevent safe participation in Study AL001-2.
	  ○ All previous participants in the AL001-1 study must be rescreened and meet all inclusion/exclusion criteria applicable to this study.
	• Meets 1 or more of the 6 behavioral/cognitive symptoms required for a diagnosis of possible behavioral variant frontotemporal dementia (bv FTD; Rascovsky 2011) or has a diagnosis of primary progressive aphasia (PPA; Gorno-Tempini 2011).
	<u>*Participant Category 2: GRN* Mutation Carriers, Asymptomatic, from AL001-1</u>
	• Prospective participant completed Study AL001-1 through the Day 43 visit and did not experience AEs that the investigator deems would prevent safe participation in Study AL001-2.
	  ○ All previous participants in the AL001-1 study must be rescreened and meet all inclusion/exclusion criteria applicable to this study. If a participant becomes symptomatic during or after Study AL001-1, they will be screened under Category 3 (symptomatic).
	<u>*Participant Category 3: GRN* Mutation Carriers, Symptomatic, New</u>
	• Is a carrier of a loss-of-function *GRN* mutation causative of FTD and knows his or her mutation status.
	• Has a Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center Frontotemporal Lobar Degeneration Behavior and Language Domains (CDR® plus NACC FTLD) global score of 0.5, 1, or 2; and 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 PPA (Gorno-Tempini 2011).
	<u>*Participant Category 4: C9orf72* Mutation Carriers, Symptomatic, New</u>
	• Is a carrier of a hexanucleotide repeat expansion *C9orf72* mutation causative of FTD and knows their mutation status
	• Has a CDR® plus NACC FTLD global score of 0.5, 1, or 2; and 1 or more of the 6 behavioral/cognitive symptoms required for a diagnosis of possible bv FTD (Rascovsky 2011), or a diagnosis of PPA (Gorno-Tempini 2011).
	Part 2 (Optional OLE)

	Participants who complete the 96-week Part 1 treatment period are eligible for continued treatment with AL001 in Part 2, provided they are able to give informed consent to continue treatment with AL001, are able to comply with the OLE study requirements, and have a study partner who can continue to assist with assessments throughout the OLE evaluation period. Part 1 participants who have been admitted to a nursing home/assisted living facility, or who have CDR® plus NACC FTLD global score >2, are not eligible for participation in the Part 2 OLE.
	Study Schema, Part 1 (Treatment Period) and Part 2 (Optional OLE) 

Study Procedures:	**Part 1 (Treatment Period)** Participants in Part 1 may be consented and screened up to 6 weeks prior to Day 1 to determine eligibility. All enrolled participants will undergo baseline evaluation with MRI, biofluid sampling for PD biomarker measurements, lumbar puncture for CSF collection, safety assessments, and several COAs. The Part 1 treatment period will be a total of 96 weeks. Study treatment (AL001 60 mg/kg) 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 12 weeks. Imaging will be performed every 24 weeks. Lumbar puncture for CSF collection will be performed every 24 weeks. Every effort will be made to follow all enrolled participants for the full 96-week treatment period, irrespective 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 96-week treatment period, participants who are eligible and provide consent will continue in Part 2 (Optional OLE) of the study. Participants who do not continue in Part 2 (Optional OLE) will return to the investigational site 10 weeks after their last dose of AL001 for final safety assessments. **Part 2 (Optional OLE)** Upon completion of the 96-week treatment period in Part 1, participants who are eligible for continued treatment in Part 2 (OLE) will receive their next regularly scheduled dose of AL001 according to the OLE administration schedule (continuation from Week 97 to Week 101). The Part 2 OLE period will be up to 96 weeks. Study treatment (AL001 60 mg/kg) will be administered IV q4w for a total of up to 25 doses. Blood sampling for safety will be performed approximately every 12 weeks. Clinical outcome assessments, including those performed by the participant and their study partner, will be conducted approximately every 24 weeks. Imaging will be performed approximately every 48 weeks. Participants who discontinue study treatment early (e.g., due to participant decision, withdrawal criteria, 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.
Safety and Tolerability Assessments:	Key safety and tolerability assessments include monitoring AEs; physical examinations; neurological examinations; vital signs and weight; electrocardiograms; clinical laboratory analyses in blood and urine; and anti-drug antibodies throughout the study.
Pharmacokinetic Assessments:	Serum and CSF samples will be collected to measure AL001 concentrations in Part 1. Serum samples will be collected to measure AL001 concentrations in the optional Part 2.
Pharmacodynamic Assessments:	Key PD assessments in Part 1 will include levels of PGRN in plasma and CSF, and Sortilin in WBCs. Key PD assessments in Part 2 will include levels of PGRN in plasma.
Clinical Outcome Assessments:	Clinical outcome assessments 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)

	• Frontotemporal Dementia Rating Scale (FRS) • Clinical Global Impression of Improvement (CGI-I) • Clinical Global Impression of Severity (CGI-S) • Color Trails Test (CTT) Part 2 • Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) • Winterlight Labs Speech Assessments (for US, UK, and Canadian participants who agree to participate in these optional assessments only)
Study Drug, Dosage, and Route of Administration:	All participants will receive AL001 (60 mg/kg) q4w intravenously (IV) over approximately 60 minutes.
Sample Size	**Part 1 (Treatment Period)** The Part 1 sample size of 40 participants was chosen based on feasibility; however, the probability of detecting at least 1 clinically significant associated finding will be explored. When the probability of a clinically significant associated finding for a single participant is 0.1%, 1%, 5%, and 10%, then with a sample size of 40 participants, the probability of detecting at least 1 clinically significant associated finding across all participants is 3.9%, 33.1%, 87.1% and 98.5% respectively. **Part 2 (Optional OLE)** It is estimated that up to approximately 40 participants from Part 1 of the study will be eligible to enroll in the optional Part 2 OLE portion of the study.
Statistical Methods:	**Part 1 (Treatment Period)** For Part 1, the statistical analysis will be performed using Statistical Analysis System (SAS) software Version 9.4 or later (SAS Institute Inc., Cary, North Carolina, USA). The statistical methods for this study will be described in a detailed Statistical Analysis Plan (SAP), which will be finalized before locking of the database. Changes from analyses planned in this protocol will be documented in the SAP. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the final clinical study report. For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of participants, mean, standard deviation, median, minimum, maximum, and 95% confidence interval [CI] where applicable). All summaries will be presented by combined participant status and dementia type at baseline (aFTD-*GRN,* FTD-*GRN* [bvFTD and PPA], FTD-*C9orf72* [bvFTD and PPA], and All Patients). Data collected for participants who failed screening and were not enrolled will not be presented in any summaries or data listings. All other data will be listed in data listings. Baseline will be defined as the last non-missing assessment, including repeated and unscheduled measurements, prior to the start of first study drug administration. All CIs will be 2-sided and performed using a 5% significance level except for PK parameters for which 90% CI and geometric mean will be used. As the objectives of Part 1 of the study are exploratory in nature no adjustments for multiplicity will be made. No formal significance testing will be performed.

	Part 2 (Optional OLE) For Part 2, no formal statistical testing will be performed. Descriptive statistics will be presented. The purpose of the OLE is to collect long-term safety and tolerability data from participants who have completed 96 weeks of treatment with AL001 under Part 1 of the study. As the objectives of the OLE are exploratory in nature no adjustments for multiplicity will be made.
Duration of Participation:	**Part 1 (Treatment Period)** • A screening period (within 6 weeks prior to Day 1) • A treatment period (96 weeks, Day 1 through Week 97) • Participants who discontinue study drug 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). o A Part 1 End of Treatment (EOT) visit will be completed by participants who discontinue study drug but remain in the study and continue to perform assessments. Part 1 EOT assessments should be completed as soon as possible after the decision is made. A Safety Follow-Up visit will be performed 10 weeks after their last study drug administration. The Safety Follow-up visit may be substituted by a scheduled visit if it occurs within the same window. o A Part 1 End of Study (EOS) visit will be completed by participants who discontinue study drug and all assessments. Part 1 EOS assessments should be completed as soon as possible after the decision is made. A Safety Follow-Up visit will be performed 10 weeks after their last study drug administration. • At Week 97, 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. o Participants who do not continue in Part 2 will complete a Part 1 EOS visit at the scheduled Week 97 timepoint. A Safety Follow-up visit will be performed 10-weeks after their last study drug administration. o Participants who continue in Part 2 will complete the Week 97 visit and continue to Part 2 (Week 101). **Part 2 (Optional OLE)** • OLE eligibility confirmation (prior to Week 101 study drug administration). • A treatment period (96 weeks, Day 101 through Week 197), or until AL001 is commercially available in the country where the participant is being treated, whichever is earlier. • Participants who discontinue study drug and/or all assessments prior to completing the 96-week Part 2 treatment period will complete a Part 2 EOS visit as soon as possible after the decision is made. A Safety Follow-Up visit will be performed 10 weeks after their last study drug administration. • At Week 197, participants who complete the Part 2 96-week OLE period will complete a Part 2 EOS visit at the scheduled Week 197 timepoint. A Safety Follow-up visit will be performed 10-weeks after their last study drug administration.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibody
ADRs	Adverse drug reactions
AE	Adverse event
aFTD-*GRN*	asymptomatic frontotemporal dementia with heterozygous progranulin gene mutations
AllFTD	ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration
ALT	Alanine aminotransferase
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-GS	Clinical Dementia Rating global score
CDR-SB	Clinical Dementia Rating sum of boxes
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 of Improvement
CGI-S	Clinical Global Impression of Severity
CI	Confidence interval
C_{max}	Maximum observed concentration
CNS	Central nervous system
COA	Clinical outcome assessment
CRA	Clinical research associate
CRFs	Case report forms
CRO	Clinical research organization
CSF	Cerebrospinal fluid
CSR	Clinical study report
C_{trough}	Trough concentration
CTT	Color Trails Test

Abbreviation	Definition
CV	Coefficient of variation
DLAE	Dose-limiting adverse event
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
FIH	First-in-human
FPI	Frontotemporal Dementia Prevention Initiative
FRS	Frontotemporal Dementia Rating Scale
aFTD	Asymptomatic frontotemporal dementia
FTD	Frontotemporal dementia
FTD-*C9orf72*	frontotemporal dementia with *C9orf72* hexanucleotide repeat expansion mutations
FTD-MND	Frontotemporal dementia with motor neuron disease
FTD-*GRN*	frontotemporal dementia with heterozygous progranulin gene mutations
FTLD	Frontotemporal lobar degeneration
FTLD-FUS	Frontotemporal lobar degeneration – immunoreactive to the fused in sarcoma protein
FTLD-TDP	Frontotemporal lobar degeneration – transactive response DNA-binding protein 43
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GRN	Progranulin gene
GUID	Global Unique Identifier
HV	Healthy Volunteer
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
iDMC	Independent Data Monitoring Committee
IEC	Independent ethics committee
IgG	Immunoglobulin G

Abbreviation	Definition
IL-6	Interleukin 6
IP	Investigational product
IRB	Institutional review board
IRT	Interactive Response Technology
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effect model of repeated measures
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NfL	Neurofilament-light chain
NIA	National Institute on Aging
OLE	Open-label extension
PD	Pharmacodynamic(s)
PE	Physical examination
PGRN	Progranulin protein
PK	Pharmacokinetic(s)
PPA	Primary progressive aphasia
q4w	Every 4 weeks
QTcF	QT interval corrected using Fridericia formula
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
SAE	Serious adverse event
SD	Standard deviation
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SDV	source data verification
Sheehan-STS	Sheehan Suicidality Tracking Scale
SUSARS	Suspected Unexpected Serious Adverse Reaction
TDP-43	Transactive response DNA-binding protein of 43 kD
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
WBC	White blood cell
WGS	Whole genome sequencing

Abbreviation	Definition
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary
WLA	Winterlight Labs Speech Assessment
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1. Background

1.1.1. Frontotemporal Dementia

Frontotemporal dementia (FTD) is a rare, early-onset form of dementia afflicting approximately 60,000 Americans (Tatton 2014) and 113,000 people in the European Union, Norway, Iceland, and Liechtenstein combined (EMA 2016). Frontotemporal dementia is typified by prominent executive dysfunction, behavioral and personality changes, and language deficits (Boxer 2013a; Boxer 2013b). It presents as 3 distinct clinical phenotypes (behavioral variant FTD [bvFTD], and 2 variants of primary progressive aphasia [PPA]: semantic variant and non-fluent variant).

The clinical FTD phenotypes include prominent social dysfunction and disinhibition, as well as language difficulties. Given the marked behavioral and personality changes of FTD and early onset of the disease, FTD patient care represents a significant burden for caregivers, families, and society (Galvin 2017). Symptoms in FTD are sometimes managed with off-label pharmacological treatment, including selective serotonin reuptake inhibitors, antipsychotics, or antiepileptics (Tsai 2014). However, no disease-modifying therapies have been approved for the treatment of FTD (Boxer 2013a; Boxer 2013b).

1.1.2. Frontotemporal Lobar Degeneration, *GRN*, and *C9orf72*

Frontotemporal lobar degeneration (FTLD) 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, transactive response DNA-binding protein of 43 kD (TDP-43); (2) FTLD-tau, with tau-positive inclusions containing fibrillar, hyper-phosphorylated tau; and (3) a small number of tau-negative, TDP-43-negative cases which are immunoreactive to the fused in sarcoma protein (FTLD-FUS) (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 approximately 40% of FTD cases, with about 10% showing an autosomal dominant pattern of inheritance (Deleon 2018), indicating a strong genetic component. *Granulin* (*GRN*) mutations account for up to 20% of all heritable FTD cases, and 5 to 10% of all cases of FTD are caused by a loss-of-function mutation in 1 allele of *GRN* (Gass 2006; Rademakers 2012; Rohlfing 2017; Cruts 2012). Heterozygous *GRN* deficiency almost invariably leads to development of FTD, making *GRN* a causal gene for the disease (Boxer 2013a; Boxer 2013b).

GRN mutations include 77 different mutations in more than 240 unrelated families, which accounts for 16% of families worldwide carrying a neurodegenerative disease-causing mutation (Ghidoni 2012) that encodes for the secreted glyocoprotein 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 2016). Progranulin 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.

C9orf72 hexanucleotide repeat expansions are also a significant contributor to FTD pathology. Expansion of a non-coding hexanucleotide repeat in *C9orf72* is the most common single cause of FTD, representing approximately 25% of familial cases and 6% of sporadic FTD cases (Ng 2015). Currently, the pathophysiology of frontotemporal dementia in carriers of *C9orf72* hexanucleotide repeat expansion mutations causative of FTD is unclear but may involve haploinsufficiency of the C9orf72 protein or abnormal dipeptide repeat proteins (data on file). The predominant clinical presentation (>80%) of *C9orf72* repeat carriers is bvFTD, with motor neuron disease (FTD-MND) or without motor neuron disease (Ng 2015).

FTD patients with *GRN* and *C9orf72* mutations exhibit a common pathology in frontotemporal degeneration associated with TDP-43 protein-related accumulation. Overlapping functional associations between *GRN* and *C9orf72* proteins include processing of TDP-43, and abnormal glial activation in patients with FTD (Ayala 2008; Zhang 2009; Mann 2017; Valdez 2017; Busch 2016; Zhang 2007; Tanaka 2013; O'Rourke 2016). Moreover, studies have suggested that TMEM106b may be a genetic modifier of both *C9orf72* and *GRN* (Gallagher 2014; van Blitterswijk 2014; Pottier 2018), suggesting that these genes may share a common pathway. Therapeutics targeted at reducing TDP-43 pathology and restoring lysosomal function may thus also slow FTD disease progression in patients with either *GRN* or *C9orf72* mutations.

1.1.3. Sortilin and AL001

Human and mouse genetic studies identified the transmembrane receptor Sortilin, encoded by the *Sortilin 1* gene, as the major negative 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 dementias.

AL001 is a recombinant humanized monoclonal antibody that binds specifically to Sortilin and is being studied for the treatment of carriers of *GRN* mutations causative of FTD and carriers of *C9orf72* hexanucleotide repeat expansion mutation causative of FTD.

1.2. Findings from Nonclinical and Clinical Studies of AL001

1.2.1. Nonclinical Studies

To support clinical studies, the toxicology and pharmacokinetics (PK) of AL001 were evaluated in single- and repeat-dose PK studies and Good Laboratory Practices (GLP) repeat-dose (4-week and 26-week) intravenous (IV) toxicology studies in cynomolgus monkeys. Overall, for the dose levels assessed, there were no significant toxicology findings in the nonclinical studies.

Refer to the AL001 Investigator's Brochure (IB) for additional details regarding nonclinical pharmacology, 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 PD of AL001 in healthy volunteers (HV) and carriers of *GRN* mutations causative of FTD. The study was conducted in two 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 pharmacokinetics (PK) and pharmacodynamics (PD) in plasma and cerebrospinal fluid (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 increase in 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 the infusion.

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 (Day 2 and Day 13). 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 different changes in CSF PGRN levels have been observed in subjects that 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 cited sampling period.

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

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

The second part of the study was conducted in two 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 repetitive dosing in symptomatic FTD carriers of a loss-of-function *GRN* mutation (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 portion 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, q2w.

Plasma PGRN Concentrations: Consistent with the literature (Meeter 2016), 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 (1 asymptomatic participant was incorrectly dosed and is not included in the summary pharmacodynamic 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 SD 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 (SAE)s, and no dose-limiting AEs. AEs have been predominantly mild to moderate in severity.

1.2.3. Study AL001-2 (Ongoing)

The current Phase 2 study, AL001-2, will evaluate the long-term safety profile of AL001 in heterozygous carriers of *GRN* or *C9orf72* mutations causative of FTD. The study will be conducted in two parts. During Part 1 (Treatment Period), participants will 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 this Phase 2 study was initiated in the third quarter of 2019. The first participant

was dosed on 27 September 2019. Target enrollment of 40 subjects is planned; up to 20 subjects with *GRN* mutations including participants from Study AL001-1 and up to 20 patients with *C9orf72* mutations. See Section 1.4.3 for a discussion of the rationale for the dosing period.

1.3. Risk/Benefit Assessment of AL001

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

1.3.1. 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.

1.3.2. 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 patients 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 or Study AL001-2 and there are no expected serious ADRs for AL001.

Immunogenicity: Subjects treated with AL001 have developed anti-drug 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 three doses of AL001 administered q2w. 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. An ADA assay for neutralizing antibodies to AL001 is under development. See the IB for more information on immunogenicity.

Adverse Events: AL001 has been generally safe and well-tolerated. There have been no deaths, no AL001-related SAEs, and no adverse events (AEs) leading to study discontinuation in the clinical trials of AL001 to date. AEs have been predominately mild to moderate in severity. Refer to the IB for a detailed summary of AEs.

> *Summary of Adverse Events – Study AL001-1 (completed):* There were no deaths and no dose-limiting adverse events (DLAEs). There was no higher incidence of treatment emergent adverse events (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 (i.e., 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 study drug in the HV cohorts: one event of rhabdomyolysis occurring in the pooled placebo cohort (attributed to [redacted] in a participant occurring 8 weeks after receiving placebo), and one event of rhabdomyolysis occurring in the SD 60 mg/kg AL001 HV cohort (attributed to [redacted] in a participant occurring 8 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 18 December 2020, a total of 26 participants had been exposed to AL001 on Study AL001-2, 24 of whom were receiving study treatment. As of the data cut off, 2 participants discontinued the study (1 participant withdrew consent, and 1 participant was discontinued at the investigator's discretion). The mean age of participants as of the data cutoff was 59.6 years (range 32-78 years).

AL001 has been generally safe and well-tolerated in this study. As of the data cutoff, there were 44 TEAEs in 18 participants (5 participants in asymptomatic FTD-*GRN*, 6 participants in symptomatic FTD-*GRN*, and 7 participants in symptomatic FTD-*C9orf72* cohorts). There have been no deaths.

The most frequently reported TEAEs across the total safety population were fall (3 participants), rash (3 participants). All other TEAEs were reported by 2 or fewer participants.

There was 1 severe SAE (venous thrombosis) that occurred in a [redacted]-year-old [redacted] participant from the symptomatic FTD-*GRN* cohort who was previously enrolled in the Phase 1 study (Study AL001-1). This SAE led to treatment discontinuation but was considered by the investigator to be not related to study drug.

All other TEAEs have been mild or moderate in severity. One TEAE of moderate severity, cellulitis (facial rash), which occurred in one participant in the FTD-*C9orf72* cohort, led to treatment interruption, and was considered not related to study drug. One participant had study treatment interrupted due to elevated lipase.

1.3.3. Potential Benefits of AL001

AL001 is being evaluated as a potential disease-modifying treatment of adults at risk for or with FTD due to a mutation in *GRN* that leads to lower levels of PGRN. AL001 is a novel recombinant human monoclonal IgG1 antibody that blocks Sortilin, decreasing the rate of PGRN clearance, and raising the concentration of PGRN. AL001 may therefore decrease the rate of neurodegeneration and clinical decline associated with FTD among patients who carry *GRN* mutations. Treatment with AL001 represents a promising therapeutic strategy, not only for FTD patients, but also for individuals who are at risk for developing FTD and while the efficacy of treatment with AL001 is still under investigation, patients with or at risk for FTD may benefit from participating in clinical trials of AL001, which are designed to evaluate a potential treatment for a disease for which there is currently no treatment or cure. All participants will receive and potentially benefit from close medical monitoring and care from qualified professionals throughout their participation in the study.

1.3.4. Benefit Risk for AL001-2 Study Participants

Frontotemporal dementia is a rare, early-onset form of dementia. Frontotemporal dementia progresses rapidly with survival after symptom onset of 3 to 14 years (Onyike and Diehl-Schmid 2013). There are currently no approved treatments for FTD (Boxer 2013a, Boxer 2013b). Participation in Study AL001-2 offers the possibility of receiving AL001, a novel recombinant human monoclonal IgG1 antibody that blocks Sortilin, for the treatment of adults at risk for or with frontotemporal dementia 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. Study participants will be randomly assigned to either AL001 or placebo.

More detailed information about the known and expected benefits and risks of AL001 may be found in the current version of the AL001 IB.

The potential benefit of AL001 to participants is described in Section 1.3.3 of the protocol, and based on completed Phase 1 study, AL001-1, which demonstrated that AL001 is associated with significant and dose dependent increases in plasma and CSF PGRN in both healthy volunteers, asymptomatic and symptomatic carriers of *GRN* mutations causative of FTD. Of note, administration of AL001 to subjects with *GRN* mutations restored CSF and plasma PGRN levels to normal. In addition, by blocking Sortilin, decreasing the rate of PGRN clearance and therefore raising the concentration of extracellular, AL001 may reduce TDP-43-associated pathology and decrease the rate of neurodegeneration and clinical decline associated with FTD among patients who carry *C9Orf72* mutations.

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 IB. Any risks to participants in AL001-2 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 IB). Adverse event and/or severe adverse event collection will occur up to 8 weeks after 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 will provide additional oversight of the study supplementing the Sponsor's careful screening, diligent monitoring and management of patient safety.

Taking the available data on the investigational therapy together with the study design and conduct, AL001 is anticipated to be generally safe, well tolerated and provide pharmacological effect at the dose of 60 mg/kg being administered. Subjects, 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 patients 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.

1.4. Rationale for the Study

1.4.1. Rationale for the Study Design

Based upon the preliminary findings of dosing-associated increases in plasma and CSF PGRN levels seen in the Phase 1 study (AL001-1), the current Phase 2 study (AL001-2) will evaluate the long-term safety profile of AL001 in aFTD-*GRN* participants, in FTD-*GRN* participants, and in symptomatic carriers of *C9orf72* hexanucleotide repeat expansion mutations causative of FTD (FTD-*C9orf72*). The study will be conducted in two parts. During Part 1 (Treatment Period), participants will receive open-label treatment with 60 mg/kg IV AL001, administered every 4 weeks (q4w) for 96 weeks. PK, PD biomarkers, and clinical outcome assessments (COAs; Section 6.9) will be evaluated as secondary and exploratory objectives. 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. The safety, PK, PD biomarker assessments and clinical outcome measures performed in this study are appropriate for this patient population and are commonly used in clinical studies in neurodegenerative diseases to assess treatment effect.

1.4.2. Rationale for Dose Selection

A suitable dose for individuals who are carriers of *GRN* and *C9orf72* mutations causative of FTD is one which is deemed to be safe and well tolerated and which is anticipated to be associated with a PD effect that is sustained in the CNS compartment. Taking into account the available nonclinical and clinical pharmacological and PD data, dose regimens were selected with the goal of restoring and sustaining CSF PGRN concentration levels in *GRN* mutation carriers to normal levels.

A dose regimen of 60 mg/kg q4w IV is used in the current study (Study AL001-2) and in the Phase 3 study (AL001-3). This dose regimen reflects the findings from the cumulative data from the Phase 1 study and the PK and PD modelling of both clinical and nonclinical data, which together indicated that an increase in CNS PGRN is more sustained at higher doses.

Please see the AL001 IB for a discussion of the safety margins for multiple doses of 60 mg/kg administered q4w.

1.4.3. Rationale for Treatment Duration

Based on the interim safety and tolerability data review by the independent Data Monitoring committee (iDMC) for this study, and based on the observed treatment effects of AL001 on biomarkers and clinical assessments in subjects treated to date, the protocol was amended to add

an optional 96-week, open-label extension period to assess the long-term safety and tolerability of AL001 in participants who have completed 96 weeks of treatment on Part 1 of the study.

The proposed mechanism of AL001 is to restore progranulin levels back to normal, thus counteracting the pathological consequences of progranulin deficiency in patients of FTD with heterozygous progranulin gene mutations (FTD-*GRN*) that cause the disease. The treatment goal of this potentially disease-modifying drug is to stop or slow down FTD progression, as measured by clinical outcome measures, and fluid and imaging biomarkers; the potential effects of AL001 on these biomarkers and outcome measures can only be fully evaluated after long-term dosing. Therefore, the current protocol has been amended to offer the option for participants to extend the AL001 treatment period from 96 weeks to 192 weeks, with the total number of doses increased from 25 doses to 50 doses. Continuation in the OLE is optional. Extending the duration of the treatment period with AL001, the first molecule shown to elevate blood and CSF progranulin levels, provides the opportunity to follow subjects 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 1 year is supported based on preliminary safety data from the chronic 26-week repeat-dose study in cynomolgus monkeys, where no AL001-related findings have been observed, and based on the safety data from the FIH study (Study AL001-1). See the AL001 IB for additional information on clinical and nonclinical studies.

1.5. Study Population

The study population includes patients with aFTD-*GRN*, patients with FTD-*GRN*, and symptomatic carriers of *C9orf72* hexanucleotide repeat expansion mutations causative of FTD (FTD-*C9orf72*).

2. STUDY OBJECTIVES AND ENDPOINTS

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

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

	Objective(s)	Endpoint(s)
Primary	The primary objective of the treatment period of the study is to evaluate the safety and tolerability of IV administration of AL001 over 96 weeks in asymptomatic and symptomatic carriers of a *GRN* mutation causative of FTD and in symptomatic carriers of a *C9orf72* mutation causative of FTD.	*Primary Safety Endpoints:* To assess the potential effect of cumulative exposure on the safety profile of AL001, the following will be evaluated by dose, such as by using tertiles of the actual dose (normalized to weight) received: • Incidence, nature, and severity of AEs and SAEs • Incidence of treatment discontinuations and study discontinuations due to AEs • Physical examination abnormalities • Neurological examination abnormalities • Changes in vital signs from baseline over time • Changes in ECGs from baseline over time • MRI abnormalities after dosing relative to baseline • Changes in clinical laboratory tests from baseline over time • Sheehan Suicidality Tracking Scale (Sheehan-STS) • Incidence of ADAs to AL001
Secondary	The secondary objectives of the treatment period of the study are to evaluate the effect of IV administration of AL001 over 96 weeks in asymptomatic and symptomatic carriers of a *GRN* mutation causative of FTD and in symptomatic carriers of a *C9orf72* mutation causative of FTD on the following:	
	Secondary PK Objective: • PK	*Secondary PK Endpoints:* • Serum concentration of AL001 at specified time points • AL001 PK parameters (if data permit) ○ C_{max} ○ C_{trough} ○ AUC_{ss}
	Secondary PD Biomarker Objectives: • Longitudinal plasma and CSF PGRN concentration levels • Longitudinal levels of Sortilin in WBCs	*Secondary PD Biomarker Endpoints:* • The overall change from baseline in PGRN in CSF • The overall change from baseline in PGRN in plasma • The overall change from baseline in Sortilin in WBCs plasma

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

	Objective(s)	Endpoint(s)
Exploratory	The exploratory objectives of the treatment period of the study are to assess the effect of IV administration of AL001 over 96 weeks in asymptomatic and symptomatic carriers of a *GRN* mutation causative of FTD and in symptomatic carriers of a *C9orf72* mutation causative of FTD on the following:	
	Exploratory PD Biomarker Objectives: • Longitudinal blood, plasma, and CSF concentration levels of exploratory biomarkers of neurodegeneration, lysosomal function, and glial activity • MRI measures to evaluate changes in the brain • Correlations among exploratory fluid PD biomarkers, imaging PD measures, and COAs	*Exploratory PD Biomarker Endpoints:* • The overall change from baseline in exploratory biomarkers of neurodegeneration, lysosomal function, and glial activity in blood, plasma, and CSF • Global and regional brain MRI atrophy measures • Correlations among exploratory fluid biomarkers, imaging measures, and COAs
	Exploratory Clinical Objectives: • Clinical progression as measured by COAs	*Exploratory Clinical Endpoints:* The overall change from baseline on the scores of the instruments in the COAs • Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center Frontotemporal Lobar Degeneration Behavior and Language Domains (Clinical Dementia Rating (CDR®) plus NACC FTLD) • Frontotemporal Dementia Rating Scale (FRS) • Clinical Global Impression of Improvement (CGI-I) • Clinical Global Impression of Severity (CGI-S) • Color Trails Test (CTT) Part 2 • Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) • Winterlight Labs Speech Assessments (WLA; for participants who agree to participate in these optional assessments only)

Abbreviations: ADA, anti-drug antibody; AE, adverse event; AUC_{ss}, area under the concentration-time curve at steady state; CDR® plus NACC FTLD, Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center Frontotemporal Lobar Degeneration Behavior and Language Domains; CGI-I, Clinical Global Impression of Improvement; CGI-S, Clinical Global Impression of Severity; C_{max}, maximum observed concentration; COA, clinical outcome assessment; CSF, cerebrospinal fluid; C_{trough}, trough concentration; CTT, Color Trails Test; ECG, electrocardiogram; FRS, Frontotemporal Dementia Rating Scale; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; *GRN*, granulin; IV, intravenous; MRI, magnetic resonance imaging; PD, pharmacodynamic; PGRN, progranulin; PK, pharmacokinetic; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SAE, serious adverse event; WBC, white blood cell.

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

	Objectives	Endpoints
Primary	The primary objective of the OLE period of the study is to assess the long-term safety and tolerability of AL001 in participants who have completed 96 weeks of treatment on Part 1 of the study.	• Incidence, nature, and severity of AEs and SAEs • Incidence of treatment discontinuations and study discontinuations due to AEs • Physical examination abnormalities • Neurological examination abnormalities • Changes in vital signs from baseline over time • Changes in ECGs from baseline over time • MRI abnormalities after dosing relative to baseline • Changes in clinical laboratory tests from baseline over time • Sheehan-STS • Incidence of ADAs to AL001
Exploratory	COAs, correlative assessments (e.g., biomarker) and other efficacy assessments conducted during the OLE are considered exploratory. The exploratory objectives of the OLE period of the study are to assess the long-term effect of AL001 in participants who have completed 96 weeks of treatment on Part 1 of the study on the following:	

	• PK	• Serum concentration of AL001 at specified time points
		• AL001 PK parameters (if data permit)
		  ○ C_{max}
		  ○ C_{trough}
		  ○ AUC_{ss}

	• Longitudinal plasma and CSF PGRN concentration levels	• The overall change from baseline in PGRN in plasma
	• Longitudinal blood, plasma, and CSF concentration levels of exploratory biomarkers of neurodegeneration, lysosomal function, and glial activity	• The overall change from baseline in exploratory biomarkers of neurodegeneration, lysosomal function, and glial activity in blood, plasma, and CSF
	• Magnetic resonance imaging (MRI) measures to evaluate changes in the brain	• Global and regional brain MRI atrophy measures

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

	Objectives	Endpoints
Exploratory (Cont.)	• Correlations among exploratory fluid PD biomarkers, imaging PD measures, and clinical outcome assessments (COAs)	• Correlations among exploratory fluid biomarkers, imaging measures, and COAs
	• Clinical progression as measured by COAs	The overall change from baseline on the scores of the instruments in the COAs • CDR® plus NACC FTLD • FRS • CGI-I • CGI-S • CTT Part 2 • RBANS • Winterlight Labs Speech Assessments (for participants who agree to participate in these optional assessments only)

Abbreviations: ADA, anti-drug antibody; AE, adverse event; AUC_{ss}, area under the concentration-time curve at steady state; Clinical Dementia Rating (CDR®) plus NACC FTLD, Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center Frontotemporal Lobar Degeneration Behavior and Language Domains; CGI-I, Clinical Global Impression of Improvement; CGI-S, Clinical Global Impression of Severity; C_{max}, maximum observed concentration; COA, clinical outcome assessment; CSF, cerebrospinal fluid; C_{trough}, trough concentration; CTT, Color Trails Test; ECG, electrocardiogram; FRS, Frontotemporal Dementia Rating Scale; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; *GRN*, granulin; IV, intravenous; MRI, magnetic resonance imaging; PD, pharmacodynamic; PGRN, progranulin; PK, pharmacokinetic; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SAE, serious adverse event.

3. INVESTIGATIONAL PLAN

3.1. Study Design

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

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

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

Part 1 (Treatment Period):

Two cohorts will be enrolled in Part 1: a *GRN* Cohort and a *C9orf72* Cohort. Both cohorts will enroll symptomatic participants with FTD; in addition, asymptomatic participants may enroll into the *GRN* Cohort, but only if they participated in the Phase 1 AL001-1 study (described in Section 1.2.2). Both asymptomatic and symptomatic carriers of a *GRN* mutation who participated in Study AL001-1 may enroll into the *GRN* Cohort if they completed dosing, the required follow-up portion of Study AL001-1 (further details are provided in Section 4.1.1), did not experience AEs that would indicate that continued dosing with AL001 would be unsafe, and meet the inclusion/exclusion criteria of Part 1of Study AL001-2. In addition, new participants who are symptomatic carriers of a *GRN* mutation will be enrolled into the *GRN* Cohort. In total, up to 20 participants will be enrolled into the *GRN* Cohort (asymptomatic and symptomatic participants). Up to 20 new symptomatic carriers of a *C9orf72* hexanucleotide repeat expansion mutation will be enrolled into the *C9orf72* Cohort. An overview of the study schema is presented in Figure 1.

Symptomatic FTD participants may enroll in Part 1 of the study if they have either 1 or more of the 6 behavioral/cognitive symptoms required for a diagnosis of possible bv FTD (Rascovsky 2011), or a diagnosis of PPA (Gorno-Tempini 2011). New symptomatic participants must also have a Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center Frontotemporal Lobar Degeneration Behavior and Language Domains (Clinical Dementia Rating (CDR®) plus NACC FTLD) global score of 0.5, 1, or 2.

Participants may be consented and screened up to 6 weeks prior to Day 1 to determine eligibility. All enrolled participants will undergo baseline evaluation with MRI, biofluid sampling for PD

biomarker measurement, lumbar puncture for CSF collection, safety assessments, and several COAs (Table 4). In Part 1, all participants will be administered open-label, IV AL001 at the investigational site (60 mg/kg, q4w) for 25 doses (over a 96-week dosing period).

Evaluation of MRI, biofluid sampling for PK and PD biomarker measurements, lumbar puncture for CSF collection, and several COAs will occur during the treatment period (the full Schedules of Assessments is provided in Table 4 and Table 5).

An independent Data Monitoring Committee (iDMC) will review safety data during the course of Part 1 of the study to provide recommendations to Alector on study conduct. The details of the iDMC are provided in Section 12.1.

The primary objective of Part 1 of the study is to assess safety and tolerability of 96-week 60 mg/kg q4w dosing of IV AL001. Secondary and exploratory objectives of Part 1 include evaluating the PK and the preliminary effect of AL001 on imaging and fluid PD biomarkers and COAs in asymptomatic and symptomatic participants. For PD biomarker evaluation, the aims are to evaluate increases in PGRN levels after repeated IV dosing of AL001 in the blood plasma and CSF of asymptomatic and symptomatic participants; to evaluate changes in PD biomarkers of neurodegeneration, lysosomal function, and glial activity; and to evaluate changes in imaging PD measures.

Part 2 (Optional Open-Label Extension):

Part 2 of the study is an optional 96-week, open-label extension to assess the long-term safety and tolerability of AL001 in participants who have completed 96 weeks of treatment on Part 1 of the study.

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.

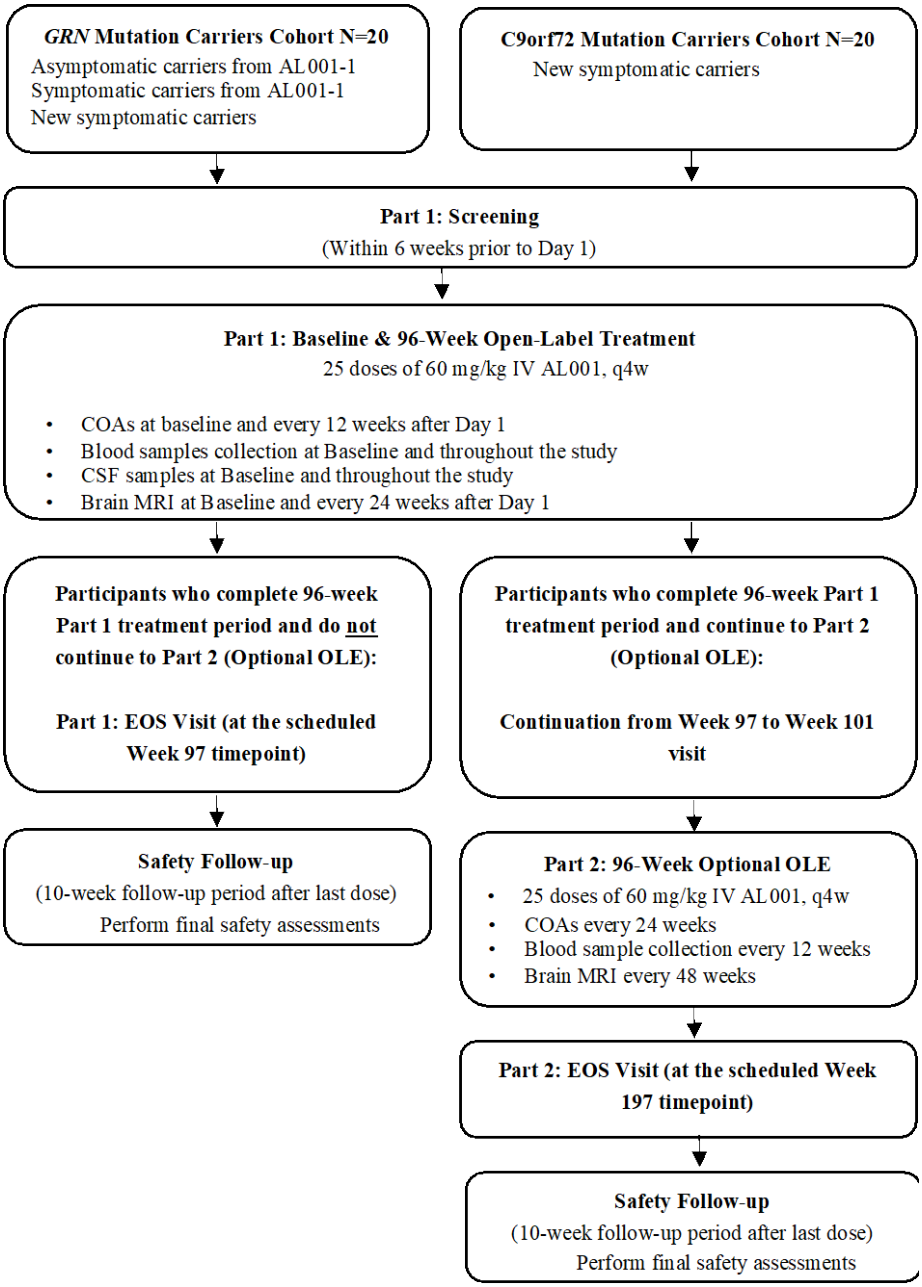
Participants who complete the 96-week Part 1 treatment period are eligible for continued treatment with AL001 in Part 2, provided they are able to give informed consent to continue treatment with AL001, are able to comply with the OLE requirements, and have a study partner who can continue to assist with assessments throughout the OLE evaluation period. Part 1 participants who have been admitted to a nursing home/assisted living facility, who have CDR® plus NACC FTLD global score >2, are not eligible for participation in the Part 2 OLE.

Continued study treatment in the optional OLE will be IV AL001 60 mg/kg, q4w (i.e., same dose and treatment regimen as in Part 1). An individual participant may continue to receive AL001 in the OLE portion of the study for up to 25 doses over a 96-week dosing period, or until AL001 is commercially available in the country where the participant is being treated, whichever is earlier. In the event that an individual's participation in the OLE will extend beyond 96 weeks because AL001 is not commercially available AL001 in their country, they may be eligible to continue to receive AL001 under another Alector protocol or program.

Evaluation of MRI, biofluid sampling for PK and PD biomarker measurements, and several COAs will continue during the optional OLE (the full Schedules of Assessments is provided in Table 4 and Table 5).

Participants will be discontinued from the OLE in the event of long-term placement in a skilled nursing facility; a CDR® plus NACC FTLD global score >2; if, in the opinion of the investigator and Alector, they are unable to follow protocol procedures; or if they develop intercurrent illness that would confound the interpretation of safety and efficacy data.

Figure 1: Overview of Study Schema



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

3.2. Study Duration

Part 1 (Treatment Period):

- A screening period (within 6 weeks prior to Day 1).
- A treatment period (96 weeks, Day 1 through Week 97).
- Participants who discontinue study drug 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 End of Treatment (EOT) visit will be completed by participants who discontinue study drug but remain in the study and continue to perform assessments. Part 1 EOT assessments should be completed as soon as possible after the decision is made. A Safety Follow-Up visit will be performed 10 weeks after their last study drug administration. The Safety Follow-up visit may be substituted by a scheduled visit if it occurs within the same window.
  - A Part 1 End of Study (EOS) visit will be completed by participants who discontinue study drug and all assessments. Part 1 EOS assessments should be completed as soon as possible after the decision is made. A Safety Follow-Up visit will be performed 10 weeks after their last study drug administration.
- At Week 97, 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 97 timepoint. A Safety Follow-up visit will be performed 10-weeks after their last study drug administration.
  - Participants who continue in Part 2 will complete the Week 97 visit and continue to Part 2 (Week 101).

Part 2 (Open-Label Extension)

- OLE eligibility confirmation (prior to Week 101 study drug administration).
- A treatment period (96 weeks, Day 101 through Week 197), or until AL001 is commercially available in the country where the participant is being treated, whichever is earlier.
- Participants who discontinue study drug and/or all assessments prior to completing the 96-week Part 2 treatment period will complete a Part 2 EOS visit as soon as possible after the decision is made. A Safety Follow-Up visit will be performed 10 weeks after their last study drug administration.
- At Week 197, participants who complete the Part 2 96-week OLE period will complete a Part 2 EOS visit at the scheduled Week 197 timepoint. A Safety Follow-up visit will be performed 10-weeks after their last study drug administration.

3.3. Description of Study Periods

3.3.1. Part 1 – Treatment Period

Screening

Participants may be consented and screened within 6 weeks prior to Day 1 to determine eligibility.

Treatment Period and Follow-up Period

The planned study treatment period will be a total of 96 weeks. AL001 60 mg/kg will be administered intravenously q4w for a total of 25 doses (up to and including Week 97). Cognitive and functional testing (Section 6.9), which may include input from the participant and study partner (study partner is described in Section 4.1.1), will be performed during screening and then every 12 weeks. Imaging will be performed during screening and then every 24 weeks. Lumbar puncture for CSF collection will be performed at screening and then every 24 weeks. Accepted windows for treatment, clinical assessments, and imaging are provided in the Schedules of Assessments (Table 4, Table 5, Table 6, Table 7, Table 8, and Table 9).

Every effort will be made to follow all enrolled participants for the full 96-week treatment period, irrespective 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 96-week treatment period, participants who are eligible and provide consent will continue in Part 2 (Optional OLE) of the study (Continuation from Week 97 to Week 101). Participants who do not continue in Part 2 (Optional OLE) will return to the investigational site 10 weeks after their last dose of AL001 for final safety assessments.

In this protocol (Study AL001-2), the term “study drug” refers to AL001.

3.3.2. Part 2 – Optional OLE

Eligibility Confirmation

There is no Screening period for participants that opt-in to continue receiving AL001 in Part 2 (Optional OLE) of the study. Participants who, after completing the 96-week treatment period in Part 1 (Week 97), and who provide informed consent to participate in Part 2 (optional OLE) and meet all the eligibility criteria for the OLE (prior to Week 101 study drug administration), may continue to receive their next regularly scheduled dose of AL001 according to the OLE administration schedule (continuation from Week 97 to Week 101).

Treatment Period and Follow-Up Period

The Part 2 OLE period will be up to 96 weeks. Study treatment (AL001 60 mg/kg) will be administered IV q4w for a total of up to 25 doses. Blood sampling for safety will be performed approximately every 12 weeks. Clinical outcome assessments, including those performed by the participant and their study partner, will be conducted approximately every 24 weeks. Imaging will be performed approximately every 48 weeks.

Participants who discontinue study treatment early (e.g., due to participant decision, withdrawal criteria, 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. Part 1 Study Population

Approximately 40 participants will be enrolled at approximately 13 investigational sites in North America and Europe. Two cohorts will be enrolled in Part 1 (Treatment Period):

- *GRN* mutation Cohort (up to 20 asymptomatic and symptomatic participants), including:
  - All asymptomatic and symptomatic participants in Study AL001-1 may be enrolled.
  - New symptomatic *GRN* mutation carriers may be enrolled.
- *C9orf72* mutation Cohort (up to 20 new symptomatic participants).

4.1.1. Inclusion Criteria – Part 1 (Treatment Period)

Prospective participants must meet all of the following criteria during the pre-study evaluation in order to be eligible to enroll in the study:

Part 1 (Treatment Period) Participant Category Inclusion Criteria:

1. Prospective participant meets all of the following criteria specific to their applicable participant category:

Participant Category 1: GRN Mutation Carriers, Symptomatic, from AL001-1

- Completed Study AL001-1 through the Day 57 visit and did not experience AEs that the investigator deems would prevent safe participation in Study AL001-2.
  - All previous participants in the AL001-1 study must be rescreened and meet all inclusion/exclusion criteria applicable to this study.
- Meets 1 or more of the 6 behavioral/cognitive symptoms required for a diagnosis of possible behavioral variant frontotemporal dementia (bvFTD; Rascovsky 2011), or has a diagnosis of PPA (Gorno-Tempini 2011).

Participant Category 2: GRN Mutation Carriers, Asymptomatic, from AL001-1

- Prospective participant completed Study AL001-1 through the Day 43 visit and did not experience AEs that the investigator deems would prevent safe participation in Study AL001-2.
  - All previous participants in the AL001-1 study must be rescreened and meet all inclusion/exclusion criteria applicable to this study. If a participant becomes symptomatic during or after Study AL001-1, they will be screened under Category 3 (symptomatic).

Participant Category 3: GRN Mutation Carriers, Symptomatic, New

- Is a carrier of a loss-of-function *GRN* mutation causative of FTD and knows their mutation status.
- Has a CDR® plus NACC FTLD global score of 0.5, 1, or 2; and 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).

Participant Category 4: C9orf72 Mutation Carriers, Symptomatic, New

- Is a carrier of a hexanucleotide repeat expansion *C9orf72* mutation causative of FTD and knows their mutation status.
- Has a CDR® plus NACC FTLD global score of 0.5, 1, or 2; and 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).

Part 1 (Treatment Period) General Inclusion Criteria:

2. 18 to 85 years of age, inclusive, at screening.
3. At screening, female prospective participants must be nonpregnant and nonlactating, and at least one 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 postmenopausal [amenorrhea duration of 12 consecutive months with no identified cause other than menopause]).
   b. Is a WOCBP and using an acceptable contraceptive method from screening until 10 weeks after the last dose of study drug. Acceptable contraception is defined as using hormonal contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm or cervical cap, or a condom. In addition, total abstinence, in accordance with the lifestyle of the participant, is acceptable.
   c. A WOCBP must have a serum pregnancy test conducted at screening. Additional requirements for pregnancy testing during and after the final dose of study treatment are located in the Schedules of Assessments (Table 4, Table 5, Table 7, and Table 9).
4. Male prospective participants, if not surgically sterilized, must agree to use acceptable contraception and not donate sperm from Day 1 until 10 weeks after the last dose of study drug. 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 (e.g. combined oral contraceptive pill) or an intrauterine device combined. In addition, total abstinence, if in accordance with the usual lifestyle of the prospective participant, is acceptable. Vasectomized male participants should have received medical assessment of surgical success.
5. Agrees not to donate blood or blood products for transfusion for the duration of the study and for 1 year after final dose of study drug.

6. Is willing and has the ability to comply with the study protocol requirements, in the opinion of the investigator.
7. Is willing and able to give informed consent. If the study participant is not competent, a legally authorized representative must provide informed consent on their behalf, and the participant must provide assent, in accordance with the local regulations, guidelines, and institutional review board (IRB) or independent ethics committee (IEC).
8. Has availability of a person ("study partner") who has frequent and sufficient contact with the participant (at least 5 hours per week of in-person contact), can provide accurate information regarding the participant's cognitive and functional abilities as well as their health throughout the study, agrees to provide information at site visits that require partner input for COA completion, and signs the necessary consent form. (Note: asymptomatic participants require the study partner at the COA visits only; symptomatic participants require the study partner at each visit).
    - 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. 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.
    - The same study partner should participate throughout the duration of Part 1 of the study. If a change in study partners during Part 1 is necessary, the Medical Monitor must be contacted.

Part 1 (Treatment Period) – Inclusion criteria applicable to those UK, US, or Canadian 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. US, UK, or Canadian participants and study partners must be proficient in English in the investigator's opinion.

4.1.2. Exclusion Criteria - Part 1 (Treatment Period)

Prospective participants who meet any of the following criteria during the pre-study evaluation will be excluded from enrolling in the study:

1. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins.
2. History of substance use disorder (drug or alcohol) within 2 years prior to the first study drug administration, with the exception of nicotine, as defined by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition criteria (American Psychiatric Association 2013).

3. Current acute illness or active infection requiring oral or IV antibiotics within 30 days prior to the first study drug administration that may affect safety assessments.
4. History of surgery or hospitalization during the 30 days prior to first study drug administration.
5. History of cancer within the last 5 years with the exception of basal cell or squamous cell carcinoma.
6. History or presence of intracranial tumor that is clinically relevant (e.g., glioma, cerebral metastasis).
7. Positive for hepatitis B surface antigen, hepatitis C virus antibodies, or human immunodeficiency virus-1 and -2 antibodies or antigen, or history of spirochetal infection of the CNS (e.g., syphilis or borreliosis).
8. Significant kidney disease as indicated by a screening creatinine clearance <30 mL/min as calculated by the central laboratory using the Cockcroft-Gault formula, which remains <30 mL/min if retested.
9. Impaired hepatic function as indicated by screening aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5 × the upper limit of normal (ULN) or total bilirubin ≥1.5 × ULN, which remains above either of these limits if retested or other abnormalities in synthetic function that are clinically significant. Note: Participants with Gilbert's syndrome are eligible to participate if approved by the Medical Monitor.
10. Unstable or clinically significant cardiovascular disease (e.g., myocardial infarction, angina pectoris, New York Heart Association Class III or more cardiac failure) within the last 2 years.
11. Uncontrolled hypertension, defined as an average systolic blood pressure ≥150 mmHg or an average diastolic blood pressure ≥95 mmHg, in an individual with hypertension.
12. History of or current abnormal ECG that is clinically significant, including atrial fibrillation, complete left bundle branch block, second- or third-degree atrioventricular block, or evidence of acute or subacute myocardial infarction or ischemia.
13. History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (e.g., severe left ventricular systolic dysfunction, left ventricular hypertrophy) or clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia). Note: Participants with premature ventricular contractions are eligible to participate.
14. Contraindication to lumbar dural puncture, including coagulopathy, concomitant anticoagulation (except for a platelet inhibitor such as aspirin), thrombocytopenia, or other factor that precludes safe lumbar puncture.
15. Dementia or a milder, symptomatic syndrome (e.g., mild cognitive impairment, mild behavioral impairment, or mild motor impairment) due to a condition other than FTD,

including, but not limited to, Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies, Huntington disease, or vascular dementia.

16. History or presence of clinically evident vascular disease potentially affecting the brain (e.g., 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 (e.g., abscess or brain tumor such as meningioma) that has the potential to affect cognitive function; or intracranial tumor that is clinically relevant (e.g., glioma, cerebral metastasis).
17. History of severe, clinically significant (persistent neurologic deficit or structural brain damage) CNS trauma.
18. Prospective participant resides in a skilled nursing facility, convalescent home, or long-term care facility at screening and requires continuous nursing care (i.e., >3 months). Participants from the Phase 1 study (AL001-1) who have since moved to one of these facilities and require continuous nursing care are not eligible to continue to this study (AL001-2).
19. Unable to tolerate MRI procedures (e.g., 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.
20. Prospective participant has a medical condition or extenuating circumstance that, in the opinion of the investigator, might compromise his or her ability to comply with the protocol-required testing or procedures or compromise the participant's well-being, safety, or clinical interpretability.

Part 1 (Treatment Period) – Medication-Related Exclusion Criteria:

The following medications are prohibited for a prespecified duration prior to study start, as indicated, and during the entire period of study participation (participants who start these medications during the study may be withdrawn from study drug):

21. Cannabinoids, benzodiazepines, and tricyclic antidepressants are prohibited, unless prescribed as a stable regimen for at least 30 days prior to study drug administration or used as premedication prior to lumbar puncture or MRI procedures; however, use is not permitted within 8 hours before any COA.
22. Any stimulant medication (e.g., amphetamine, dextroamphetamine, dexmethylphenidate, lisdexamfetamine, methylphenidate) is prohibited unless prescribed as a stable regimen for at least 90 days prior to study drug administration.
23. 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 (participation in Study AL001-1 does not apply to this criterion).

24. Any experimental vaccine or gene therapy; routinely recommended vaccinations are allowed as well as any vaccine against SARS-CoV-2 administered under an Emergency Use Authorization.
25. A drug from a clinical study (other than AL001-1) within 30 days prior to drug administration in the current study (study drug administration); use of any experimental oral therapy within 30 days or 5 half-lives prior to study drug administration, whichever is greater; use of any biologic therapy within 90 days or 5 half-lives prior to study drug administration, whichever is greater; or any other investigational treatment within 5 half-lives or 90 days prior to study drug administration, whichever is longer.
26. Typical antipsychotic or neuroleptic medication within 6 months of study drug administration except as brief treatment for a nonpsychiatric indication (e.g., emesis).
    a. Use of atypical antipsychotic medications or use of pimavanserin is allowed if treated with a stable regimen for at least 90 days prior to study drug administration.
27. Anti-coagulation (e.g., coumadin, heparinoids, apixaban) medications within 90 days of study drug administration. Note: Use of aspirin or antiplatelet medication is allowed.
28. Systemic immunosuppressive therapy or anticipated to be needed during the study.
    a. Use of prednisone of ≤10 mg/day or an equivalent corticosteroid is allowed if stable for at least 90 days prior to study drug administration and hemoglobin >9 g/dL, white blood cell (WBC) count >3000/mm^3, absolute neutrophil count >1500 /mm^3, and platelet count >100 000/mm^3.
29. Chronic use of opiates or opioids (including long-acting opioid medication) within 90 days of study drug administration.
    a. Intermittent short-term use (<1 week) of short-acting opioid medications for pain is permitted except within 2 days or 5 half-lives (whichever is longer) prior to any COA.
30. Chronic use of barbiturates, or hypnotics from 90 days prior to study drug administration.
    a. Intermittent short-term (<1 week) use of buspirone or short-acting hypnotic medication for sleep or anxiety is allowed except within 2 days or 5 half-lives (whichever is longer) prior to any clinical outcome assessment.

Part 1 (Treatment Period) – Exclusion criteria applicable to those US, UK, or Canadian participants participating in the optional WLA only:

1. Has clinically significant vision impairment (corrected vision is acceptable).
2. Has clinically significant hearing impairment (use of hearing aids is acceptable).

4.2. Part 2 Study Population

Up to approximately 40 participants from Part 1 of the study will be eligible to enroll in Part 2 of the study (Optional OLE). Enrollment in Part 2 is optional for the participant, and at the discretion of the investigator.

4.2.1. Inclusion Criteria - Part 2 (Optional OLE)

The OLE is optional for participants who complete Part 1 of the study. Participants who complete Week 97 of Part 1 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 their behalf, and the participant must provide assent, in accordance with the local regulations, guidelines, and institutional review board (IRB) or independent ethics committee (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, agree to provide information at site visits that require partner input for COA completion, and sign the necessary consent form. (Note: asymptomatic participants require the study partner at the COA visits only; symptomatic participants require the study partner at each visit).
    - The study partner must have sufficient cognitive capacity to accurately report upon the participant's behavior, cognitive, and functional abilities. 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.
    - 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.

4.2.2. Exclusion Criteria - Part 2 (Optional OLE)

Part 1 participants are not eligible for continued treatment with AL001 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 (i.e., >3 months).
2. Part 1 participant has a CDR® plus NACC FTLD global score >2 during Part 1.
3. Part 1 participant has a medical condition or extenuating circumstance 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. Withdrawal of Participants from Study Drug 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. A Study Discontinuation section of the electronic case report form (eCRF) must be completed for all enrolled participants only.

4.3.1. Part 1 (Treatment Period)

4.3.1.1. Withdrawal from Study Drug (Part1)

A participant may be discontinued from study drug 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 drug 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 investigator' opinion, requires withdrawal from the study drug
5. Serum aminotransferase levels (ALT or AST) >3 × ULN AND total bilirubin >2 × ULN without an alternative explanation
6. Anaphylaxis
7. Infusion-related or injection-related reaction despite adequate premedication for an initial occurrence of a moderate to severe infusion-related reaction (Section 5.1.2) or if the participant experiences any of the following events: mucosal tissue involvement, airway compromise, or symptomatic hypotension with systolic blood pressure <90 mm Hg measured in the supine position
8. Occurrence of an intercurrent illness that, in the investigator's opinion, will affect assessments of clinical status or safety to a significant degree
9. Use of a nonpermitted concomitant medication per Section 4.1.2 (as appropriate)
10. Pregnancy
11. Discretion of the investigator

If a participant is withdrawn from study drug due to an AE or 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 drug for any reason except participant withdrawal of consent and in case of medical emergency. If a participant is discontinued because of an AE or SAE, the event will be followed up until it is resolved. Any participant may withdraw his or her consent at any time.

All participants who discontinue study drug 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 97). Study staff will follow-up to aid in this goal.

The reason for the participant's early discontinuation of study drug will be specified in the participant's source documents and on the eCRF. A Part 1 End of Treatment (EOT) visit will be completed by participants who discontinue the study drug but remain in the study and continue to perform assessments. Part 1 EOT assessments should be completed as soon as possible after the decision is made. A Safety Follow-Up visit will be performed 10 weeks after their last study drug administration. The Safety Follow-up visit may be substituted by a scheduled visit if it occurs within the same window.

4.3.2. Withdrawal From Study (Part 1)

A participant may be discontinued from the study (including study drug and all assessments) 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 discontinuation:

1. Participant withdrawal of consent
2. Lost to follow-up
3. Discretion of the investigator
4. Administrative or other reasons (e.g., premature termination of the study by Alector)

All Part 1 participants who discontinue the study drug and all assessments prior to the scheduled Week 97 visit should be encouraged to return to the site for a Part 1 EOS visit. 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 the participant's last study drug administration. Reasonable attempts will be made by the investigator to obtain reasons for participant withdrawals (e.g., 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. Part 2 (Optional OLE)

4.4.1. Criteria for Withdrawal of Participants in Part 2

A participant may be discontinued from Part 2 of the study (including study drug and all assessments) 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 Part 2 study discontinuation:

1. Long-term placement in a skilled nursing convalescent home, or long-term care facility at screening and requires continuous nursing care. (i.e., >3 months)
2. If, in the opinion of the investigator and Alector, they are unable to follow protocol procedures

3. If they develop intercurrent illness that would confound the interpretation of safety and efficacy data
4. CDR® plus NACC FTLD global score >2 during Part 2
5. AL001 is commercially available in the country where the participant is being treated
6. Participant withdrawal of consent
7. Lost to follow-up
8. Discretion of the investigator
9. Administrative or other reasons (e.g., premature termination of the study by Alector)
10. Participant is noncompliant with the protocol
11. Participant has a serious or intolerable AE that, in the investigator' opinion, requires withdrawal from the study drug
12. Serum aminotransferase levels (ALT or AST) >3 × ULN AND total bilirubin >2 × ULN without an alternative explanation
13. Anaphylaxis
14. Infusion-related or injection-related reaction despite adequate premedication for an initial occurrence of a moderate to severe infusion-related reaction (Section 5.1.2) or if the participant experiences any of the following events: mucosal tissue involvement, airway compromise, or symptomatic hypotension with systolic blood pressure <90 mm Hg measured in the supine position
15. Occurrence of an intercurrent illness that, in the investigator's opinion, will affect assessments of clinical status or safety to a significant degree
16. Use of a nonpermitted concomitant medication per Section 4.1.2 (as appropriate)
17. Pregnancy

All Part 2 participants who discontinue the study drug and/or all assessments prior to the scheduled Week 197 visit should be encouraged to return to the site for a Part 2 EOS visit. Part 2 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 drug administration. Reasonable attempts will be made by the investigator to obtain reasons for participant withdrawals (e.g., 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.

4.5. Replacements (Part 1 Only)

Participants who do not meet all eligibility criteria at screening or who qualify at screening but are not enrolled within the screening period may be reconsented, assigned a new screening number, and rescreened (see Section 6.2).

Participants who withdraw from the study may be replaced at the discretion of Alector and in consultation with the investigator.

Note: the optional OLE (Part 2 of the study) is open to any eligible participant from Part 1; thus, replacing participants who leave the OLE is not applicable.

5. STUDY TREATMENTS

This is an open-label study; all participants will receive AL001 (Part 1 treatment period and Part 2 optional OLE).

Each participant who provides informed consent will be assigned a screening number that uniquely identifies the participant. It is the responsibility of the investigator to ensure each participant is eligible for the study prior to enrollment. Participants who complete Part 1 will retain their unique screening number if they participate in Part 2. Alector will maintain a central screening log and utilize an electronic data capture (EDC) and Interactive Response Technology (IRT) systems to implement enrollment, to assess current inventories of AL001, to initiate necessary resupply of drug and to document discontinuation of drug.

5.1. Treatments Administered

Part 1(Treatment Period)

All participants will receive AL001 (60 mg/kg IV) on Day 1, and then q4w for a total of 25 doses over a 96-week period.

Part 2 (Optional OLE)

Participants in the OLE will receive AL001 60 mg/kg IV q4w. An individual participant may continue to receive AL001 on the OLE portion of the study for up to 25 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.

5.1.1. Administration Instructions

AL001 will be administered intravenously over approximately 60 minutes at the investigational site by study-trained clinic staff under the supervision of the investigator or their designee, or by a home health service, as applicable (See Appendix 3). Dosing solution preparation instructions will be provided separately in a Pharmacy Manual.

Documentation of study drug administration will be recorded in the source documentation and documented in the eCRF.

The investigator is responsible for the education of study staff in the correct administration of the study drug.

Participants will be monitored for at least 60 minutes after the end of infusion (Section 5.1.2) and completion of all activities scheduled for that visit day and discharged at the discretion of the investigator.

5.1.2. Infusion-Related and Injection-Related Reactions

All participants 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 will be resumed at half the most recently used rate (e.g., 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 (e.g., 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 should 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 blood pressure <90 mm Hg measured in the supine position.

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

5.2. Identity of Investigational Product

5.2.1. Study Drug Formulation

The study drug (AL001) is provided as a liquid solution formulated at a concentration of 50 mg/mL in an aqueous solution containing AL001 (human recombinant anti-human Sortilin IgG1 monoclonal antibody) in 20 mM histidine / histidine HCL, 7.5% (w/v) sucrose and 0.02% (w/v) polysorbate-80 at pH 5.5.

5.2.2. Study Drug Packaging and Labeling

The container closure system for AL001 study drug consists of a 20R Type I (EP-compliant) clear glass vial, with a coated bromobutyl rubber stopper and an aluminum crimp seal with blue flip-off cap. Each single-use vial will contain at least[redacted] mL of a [redacted] mg/mL solution of AL001 study drug.

AL001 will be labeled to meet applicable requirements of the Food and Drug Administration (FDA) as well as the EU Guideline for Good Manufacturing Practice for Investigational Medicinal Products (Annex 13), and other local requirements.

5.3. Management of Clinical Supplies

Specific instructions about the storage, preparation, and administration of AL001 are provided in the Pharmacy Manual. Additional information about AL001 is provided in the IB and on the Certificate of Analysis.

5.3.1. Study Drug Supply

Alector will supply AL001 to the investigational sites, as detailed in the Pharmacy Manual.

5.3.2. Study Drug Storage

Study drug will be shipped at a temperature of 2°C to 8°C.

Upon receipt at the investigational site, the study drug shall be stored securely under controlled conditions until use, in a refrigerator, set to maintain 2°C to 8°C. 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 study drug while they are at their investigational facility.

5.3.3. Study Drug Accountability

The investigational site will maintain accurate records of receipt of all study drug, including dates and condition of receipt. In addition, accurate records will be kept (including the initials of the person dispensing the study drug) regarding when and how much study drug is dispensed and used by each participant in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled and retained or destroyed according to applicable regulations.

5.3.4. Study Drug Return or Disposal

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

5.4. Misuse for Illegal Uses

AL001 is supplied for use only in this clinical study and should not be used for any other purpose.

5.5. Blinding

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

5.6. 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), March 2019 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 accepted 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.

Any restricted medication must have been stopped as required by the study inclusion and exclusion criterion (Section 4.1.1 and Section 4.1.2, respectively); participants who start these medications during the study may be withdrawn from study drug at the discretion of the Medical Monitor.

6. STUDY ASSESSMENTS AND PROCEDURES

Before performing any study procedures, all potential participants and study partners will sign an informed consent form (ICF). If the study participant is not competent, a legally authorized representative must provide informed consent on their behalf, and the 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 participants. 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 4,Table 5) and Schedule of PK, Immunogenicity, and PD Biomarker Sample and Imaging Assessments (Table 6).Timing and frequency of all assessments and procedures for Part 2 are presented in the Schedules of Assessments (Table 7 and Table 8) and Schedule of PK, Immunogenicity, and PD Biomarker Sample and Imaging Assessments (Table 9). Asymptomatic participants require the study partner at the COA visits only; symptomatic participants require the study partner at each visit.

Adaptations to visits and procedures under the exceptional circumstance of COVID-19 pandemic are detailed in Appendix 3.

6.1. Timing of Study Drug Administration

Pre-dose Study Procedures and Assessments:

- Perform COAs prior to any potentially stressful procedure (e.g., blood collections, lumbar punctures, imaging)
- PE, or limited or symptom-directed examination
- Neurological examination, or limited or symptom-directed examination
- Vital signs and weight, including blood pressure (BP), pulse, body temperature, and respiratory rate
- Triplicate 12-lead ECG
- Obtain blood and urine samples for chemistry, hematology, coagulation, serology, pregnancy testing, and urinalysis.
- Obtain blood samples for ADAs
- Obtain blood samples for PK and PD
- Obtain blood sample for whole genome sequencing (WGS) (Part 1 only)
- Collect CSF samples via lumbar puncture for PK and PD (Part 1 only)
- Perform MRI
- Perform Sheehan Suicidality Tracking Scale (Sheehan-STS)
- Review of concomitant medication(s)

- Record any AEs and SAEs

Dosing Procedures:

- AL001 will be administered to participants per institutional practice (Section 5.1).

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 screen failed. Rescreening may be allowed after approval from the Medical Monitor. Participants who rescreen after the screening period must be reconsented with a new screening number, and the screening assessments must be repeated. The participant may not be required to repeat the MRI imaging or CSF screening assessment, if performed within 3 months prior to screening. Clinical outcome assessments performed within 8 weeks prior to screening may not be required to be repeated after approval from the Medical Monitor.

Those aFTD-*GRN* and FTD-*GRN* participants who have completed Study AL001-1 (described in Section 1.2.2) may enroll in this study. Participants must be rescreened after completion of Study AL001-1 and meet all inclusion/exclusion criteria applicable to this study. The participant may not be required to repeat the imaging (MRI) or CSF baseline assessment if performed within 3 months prior to screening. The participant may not be required to repeat the safety and tolerability assessments, if performed within 6 weeks prior to screening.

All participants are not required to report WGS results, and there is no time restriction for reporting.

Rescreening is not applicable for Part 2 of the study.

6.3. Sample Collections

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

Unused portions of PK, PD, and/or exploratory PD biomarker 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 PD biomarkers (e.g., associated with efficacy, AEs, or disease

progression), further clarification or characterization of the disease, further evaluation of the study drug's effects, and/or development of assays (e.g., PD biomarker or diagnostic assays).

6.4. Cerebrospinal Fluid Sampling

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

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

6.5. Safety and Tolerability Assessments

Safety and tolerability assessments include monitoring AEs; PEs; neurological examinations; vital signs and weight; ECGs; clinical laboratory analyses in blood and urine; MRIs; Sheehan-STS; 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 drug which 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 7.1.

6.5.2. Concomitant Medications

All medication history and use of concomitant medications will be collected and recorded in the eCRF as detailed in Section 5.6.

6.5.3. Demographics

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

For US, UK, and Canadian participants who will be performing the optional WLA, additional demographic information will be collected (ethnicity, number of years of education, first language, when they learned English [if English is not their first language], how long they have been speaking English consistently [if English is not their first language], country of birth, and year of immigration to Canada/United States/United Kingdom [if applicable]).

Alector is collaborating with the 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 United States 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.

For AL001-2 study participants who are also participating in the GENFI or AllFTD, they will have the option to have their NIA GUID collected by the investigational site personnel and recorded in the AL001-2 EDC system. For AL001-2 study participants who are not participating in GENFI or AllFTD, they will have the option for the investigational site personnel to assign a NIA GUID and recorded it in the AL001-2 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 at screening prior to study drug administration in the eCRF.

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

6.5.5. Physical Examinations

A complete PE includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, and gastrointestinal systems. Breast, genital, and rectal examinations are not required, unless warranted in the opinion of the health care provider. Limited examinations should include cardiovascular, respiratory, and gastrointestinal systems. Symptom-directed PEs may also include any other pertinent system as required. The examination will be performed by a physician or by a nurse practitioner or physician's assistant under the supervision of a physician.

Complete or limited or symptom-directed examinations will be performed at time points indicated in the Schedule of Assessments. For visits with study drug administration, this should be completed prior to the study drug infusion. Additional examinations may be completed as clinically indicated.

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

Height (cm) will be measured at screening.

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. Limited or symptom-directed examinations will be performed at all other specified time points. A symptom-directed neurological examination should focus on the affected organ system or body area.

For visits with study drug administration, this should be completed prior to study drug infusion. Additional examinations may be completed as clinically indicated.

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

6.5.7. Vital Signs and Weight

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

Pulse rate, BP, body temperature, and respiratory rate should be obtained per institutional practices.

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.

Weight (kg) will be collected 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 ≥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.

6.5.9. 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 3.

For any laboratory test value outside the reference range that the investigator considers clinically significant, the investigator will follow the instructions in Section 7.3.

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 3: Laboratory Assessments

<table>
<tr><th>Chemistry</th><th>Coagulation</th><th>Hematology</th><th>Serology</th></tr>
<tr><td rowspan="3">Total bilirubin
Direct bilirubin
Alkaline phosphatase
gammaGT
AST
ALT
LDH
Creatine kinase
Creatinine [a]
Urea
Uric acid
Cholesterol
HDL
LDL
Triglycerides
Total protein
Albumin
Glucose
Bicarbonate
Inorganic phosphate
Sodium
Potassium
Calcium
Chloride
Magnesium
Lipase
Apolipoprotein B100</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 [b]
ANC [b]</td><td>anti-HCV
anti-HIV
HIV antigen
HBsAg
Total hepatitis B core antibody</td></tr>
<tr><td colspan="2">Urinalysis</td><td>Pregnancy Test</td></tr>
<tr><td colspan="2">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>Serum β-hCG or urine pregnancy test [c]</td></tr>
</table>

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

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

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

[c] All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits prior to study drug administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[d] Microscopic examination of the sediment if blood, protein, leukocytes esterase, or nitrite are positive on the dipstick.

6.5.10. Sheehan Suicidality Tracking Scale

The Sheehan-STS (described in Appendix 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. An AE should only be recorded if the investigator makes an evaluation and deems there to be suicidal ideation or behavior.

6.5.11. Anti-Drug 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 5.1.2 and Section 7.9). A sample of blood should be obtained for serum PK and ADA assessment of AL001, and testing should be performed for C-reactive protein, tryptase, and Interleukin 6 (IL-6).

6.6. Pharmacokinetic Assessments

6.6.1. Serum Pharmacokinetic Samples

Blood serum samples will be collected for assessment of serum concentrations of AL001. All PK samples should be collected from the arm that is not used for the infusion on day of study drug administration.

6.6.2. Cerebrospinal Fluid Pharmacokinetic Samples

Cerebrospinal fluid samples will be assessed for concentration of AL001 in Part 1 only. See Section 6.4 for details of CSF sampling.

6.7. Pharmacodynamic Biomarker Assessments

6.7.1. Progranulin Plasma Samples

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

6.7.2. Cerebrospinal Fluid Pharmacodynamic Samples

Cerebrospinal fluid samples will be evaluated for levels of PGRN in Part 1 only. See Section 6.4 for details of CSF sampling.

6.7.3. Whole Blood Samples

Whole blood samples will be collected for evaluation of levels of Sortilin in WBCs and for evaluation of other analytes in Part 1 only.

6.7.4. Exploratory Pharmacodynamic Biomarker Assessments

6.7.4.1. Other Exploratory Pharmacodynamic Biomarker Samples

Exploratory whole blood, plasma, and CSF PD biomarker samples will be collected for evaluation for neurodegeneration (e.g., neurofilament light chain [NfL], [redacted]), lysosomal function (e.g., cathepsins), and glial activity (e.g., YKL-40, IL-6), evaluation of messenger ribonucleic acid (mRNA) expression in peripheral cells, and to potentially evaluate levels of other analytes relevant to disease biology and response to AL001. CSF PD biomarker samples will be collected in Part 1 only.

6.7.4.2. Magnetic Resonance Imaging

MRI 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, brain perfusion (measured by [redacted] MRI), fractional anisotropy, [redacted]).

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

6.8. Pharmacogenomic Assessments

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

Genomics is increasingly informing researchers' understanding of disease pathobiology. Whole genome sequencing provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. 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. Clinical Outcome Assessments – Neurocognitive and Functional Tests

The following neurocognitive and functional tests (described in Appendix 2) will be performed. Neurocognitive and functional tests will be performed prior to study drug administration (if applicable) and prior to any stressful procedures (e.g., blood collections, imaging).

- 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 of Improvement (CGI-I)
- Clinical Global Impression of Severity (CGI-S)
- Color Trails Test (CTT) Part 2
- Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
- WLA (US, UK, and Canadian participants who are proficient in English and who agree and are eligible to participate in the optional assessments only, refer to Appendix 2).

A tablet will be used to collect data for the electronic COAs. A few COAs will be completed on paper and entered into the eCRF. Specific information on the collection and data entry of neurocognitive and function tests will be provided in a separate manual. Adaptations to visits and procedures under the exceptional circumstance of COVID-19 pandemic are detailed in Appendix 3.

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

6.10. Unscheduled Visits

Unscheduled visits may occur at any time while the participant is enrolled in the study.

6.11. Part 1 End of Treatment Visit

Participants who discontinue study drug 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 drug but remain in Part 1 of the study and continue to perform all assessments (Section 4.3.1.1). 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.

6.12. End of Study Visit

6.12.1. Part 1 End of Study Visit

Participants who discontinue study drug and all assessments prior to completing the 96-week Part 1 treatment period (Section 4.3.2) will complete a Part 1 EOS visit as soon as possible after the decision 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 97, 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 97 timepoint. Participants who continue in Part 2 will complete the Week 97 visit and continue to Part 2 (Week 101).

6.12.2. Part 2 End of Study Visit

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

At Week 197, participants who complete the 96-week Part 2 OLE period will complete a Part 2 EOS visit at the scheduled Week 197 timepoint.

6.13. Safety Follow-up Visit

A Safety Follow-up visit will be performed 10-weeks following the last dose of AL001. The Safety Follow-up visit may be substituted by a scheduled visit if it occurs within the same window.

7. ADVERSE EVENTS

The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

7.1. Definitions of Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

An AE is defined as any untoward medical occurrence in a participant enrolled into this study regardless of its causal relationship to study drug. Participants will be instructed to contact the investigator at any time after informed consent signature if any symptoms develop. Study participants should be instructed to report all AEs to the investigator. All AEs must be appropriately documented in the participant's original source documents and on the eCRFs. Investigators should report the diagnosis rather than list symptoms, whenever possible.

An AE does not include the following:

- Elective medical or surgical procedures planned prior to the start of study treatment (e.g., hip replacement surgery) that did not result from a worsening of a previous condition. The condition that led to the procedure may be an AE and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected at the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for study drug administration per institutional guidelines, elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae.
- 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. It is considered to be a pre-existing medical condition and should be documented on the medical history eCRF. However, deterioration of a medical condition or new or worsened clinically significant abnormality during the study should be reported as an AE.
- Any AE that began during the Phase 1 study (AL001-1) and was ongoing at the time of enrolling in this study (AL001-2) will not be considered an AE, but medical history.

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported in the established time frames.

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

7.2. Serious Adverse Events

An SAE is defined as any AE that fulfills one 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
- Is a congenital anomaly/birth defect
- Is an important medical event that may jeopardize the participant or may require medical intervention to prevent one of the outcomes listed above

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

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.

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

7.3. 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 (e.g., 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.

7.4. Assessment of Causality

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

Relationship to Study Drug	Comment
Related	There is reasonable possibility that the event may have been caused by the study drug (e.g., 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 the study drug.

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 drug?"

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.

7.5. Reporting Adverse Events

All AEs and SAEs must be recorded and reported, regardless of cause or relationship, that occur after the participant signs informed consent 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. Definitions describing what is and is not considered an AE are provided in Section 7.1.

Information to be collected includes the following:

- Event term
- Time and date of onset
- Investigator-specified assessment of severity and relationship to study drug
- Time of resolution of the event

- Seriousness
- Any required treatment or evaluations
- Outcome

The Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1 or later will be used to code all AEs.

7.6. Reporting Serious Adverse Events

In the event of any SAE reported or observed during the study, the investigational site is immediately required to complete the AE eCRF within the EDC system, indicating the AE is serious, and at least 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 [redacted] according to the instructions provided in the Study-Specific Regulatory Binder

The participant's condition will be followed up by the investigator or designated sub-investigator until resolution of the condition, as described in Section 7.8. 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 will be notified and provided with all relevant information.

It is the investigator's responsibility to report all SAEs to Alector (covered in Section 11.6), and it is Alector's responsibility to ensure that all safety reporting obligations are carried out in compliance with current legislation for expedited reporting of SAEs (including Suspected Unexpected Serious Adverse Reaction (SUSARS)).

7.6.1. Protocol-Specific Disease Progression Adverse Event and Serious Adverse Event Reporting Requirements

Disease progression in this study is measured via the 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.

7.7. 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 World Health Organization (WHO)

Toxicity Grading Scale, March 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.

It should be pointed out 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. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode. When the intensity of an AE changes more than once a day, the maximum severity for the event should be listed. If the intensity changes over a number of days, these changes should be recorded separately (e.g., as having distinct onset dates).

7.8. 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 event can be attributed to agents other than the study drug 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, Alector (or designee) should be notified if the investigator becomes aware of any SAE that is believed to be related to prior study drug.

7.9. 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 5.1.2 of this protocol and in the IB.

7.10. 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.

7.11. Special Situations

Special situations are non-standard medical conditions that provide valuable information about an investigational product (IP) even when they do not occur in association with an AE or medical condition, and therefore should be reported. All special situations should be reported using a paper Serious Adverse Event Report Form and emailed to [redacted] according to the instructions provided in the Study-Specific Regulatory Binder.

Special situations are defined as below:

- Overdose: This refers to the administration of a quantity of 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.
- Abuse: This corresponds to the persistent or sporadic, intentional excessive use of IP, which is accompanied by harmful physical or psychological effects.
- Medication error: A medication error is any dose of study treatment given to a subject or taken by a subject that differs from the dose described in the protocol. Any medication error, with or without associated AEs, must be promptly recorded in the eCRF. Medication errors without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the medication error, these should be reported on relevant AE/SAE sections in the eCRF. 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.

7.12. Pregnancy

Female participants must be instructed to discontinue all study drugs 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 the event 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 [redacted] according to the instructions provided in the Study-Specific Regulatory Binder.

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

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

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 drug until Part1/Part 2 EOS or Safety Follow-up visit, whichever is later.

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 drug, must be promptly reported to Alector (or designee).

8. STATISTICAL METHODS AND CONSIDERATIONS

This section describes the statistical methods to be used for the analysis of the data from the study. Additional information is provided in the Statistical Analysis Plan (SAP).

8.1. Sample Size Estimations

Part 1 (Treatment Period)

The primary objective of Part 1 of the study is to assess the safety profile of repeat dosing of AL001 in asymptomatic and symptomatic participants. Descriptive statistics will be used to assess clinically significant associated findings (for example, study drug related AEs leading to study drug discontinuation or study drug-related SAEs). The Part 1 sample size of 40 participants was chosen based on feasibility; however, the probability of detecting at least 1 clinically significant associated finding will be explored. When the probability of a clinically significant associated finding for a single participant is 0.1%, 1%, 5%, and 10%, then with a sample size of 40 participants, the probability of detecting at least 1 clinically significant associated finding across all participants is 3.9%, 33.1%, 87.1% and 98.5% respectively.

Part 2 (Optional OLE)

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

8.2. Analysis Populations

Part 1 (Treatment Period)

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

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

Safety Analysis Population: The safety analysis population will consist of all participants who received at least 1 dose of AL001. The safety analysis population will be used for safety summaries.

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

Full Analysis Population: The full analysis population will include all participants in the safety analysis population who had both a baseline and at least 1 post-dose assessment. The full analysis population will be used for all PD and PD biomarker summaries.

Part 2 (Option OLE)

Part 2 analyses will include all participants who received at least 1 dose administration in Part 2.

8.3. Description of Subgroups to be Analyzed

Except for safety endpoints, all other study endpoints specified above will be summarized by *GRN* mutation carriers vs *C9orf72* mutation carriers. Additional subgroups may be summarized as exploratory.

8.4. Statistical Analysis Methodology

The main statistical analysis will be performed on Part 1. The statistical analysis will be performed using SAS software Version 9.4 or later (SAS Institute Inc., Cary, North Carolina, USA). The statistical methods for this study will be described in a detailed Statistical Analysis Plan (SAP), which will be finalized before locking of the database. Changes from analyses planned in this protocol will be documented in the SAP. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the final clinical study report (CSR).

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of participants, mean, standard deviation [SD], median, minimum, maximum, and 95% confidence interval [CI] where applicable). All summaries will be presented by combined participant status and dementia type at baseline (aFTD-*GRN,* FTD-*GRN* [bvFTD and PPA], FTD-*C9orf72* [bvFTD and PPA], and All Patients).

Part 1 (Treatment Period)

In Part 1, data collected for participants who failed screening and were not enrolled will not be presented in any summaries or data listings. All other data will be listed in data listings. Baseline will be defined as the last non-missing assessment, including repeated and unscheduled measurements, prior to the start of first study drug administration.

In Part 1, all CIs will be 2-sided and performed using a 5% significance level, except for PK parameters, for which 90% CI and geometric mean will be used. As the objectives of the study are exploratory in nature no adjustments for multiplicity will be made.

No formal significance testing will be performed.

Part 2 (OLE)

For Part 2, no formal statistical testing will be performed. Descriptive statistics will be presented for Part 2 separately from Part 1. The purpose of the OLE is to collect continued long-term (up to 96 weeks) safety and tolerability data from participants who have completed Part 1 of the study. As the objectives of the OLE are exploratory in nature no adjustments for multiplicity will be made.

8.4.1. Study Population

All study population summaries will be presented using the enrolled population.

8.4.1.1. Disposition of Participants

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

8.4.1.2. Protocol Deviations

A protocol deviation occurs when the participant, investigator, or Alector fails to adhere to protocol requirements. Major protocol deviations for this study are described in Section 12.4.2.

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

8.4.2. Analysis of Primary Safety Endpoints

All safety summaries will be presented using the safety analysis population.

8.4.2.1. Demographic, Baseline, and Background Characteristics

Demographics (including but not limited to age, sex, and race, if allowable per local regulatory authorities) and baseline and background characteristics will be presented in summary tables. Qualitative data (e.g., medical history, diagnostic characterization) will be summarized in contingency tables, and quantitative data (e.g., age) will be summarized using quantitative descriptive statistics.

All genotype data will be presented in a summary table.

8.4.2.2. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO-DD, March 2019 or later.

A medication will be considered as concomitant if the end date and time of administration is after start of administration of study drug. If the date and time of administration contains partial information such that the attribution of concomitant administration cannot be ruled out, then it will be considered as concomitant. A medication will be considered as prior if the start and stop date and time of administration is prior to the start of administration of study drug. A medication started prior to study drug and continuing during the study will be considered as concomitant.

All prior and concomitant medications data will be summarized by anatomical therapeutic chemical classes and generic names. Separate summaries will be presented for prior and concomitant medications.

8.4.2.3. Study Drug Administration

Study drug administration data will be summarized by number of doses received and total dose received. The overall treatment compliance will be calculated based on dose interruptions/discontinuations.

8.4.2.4. Adverse Events

Adverse events will be recorded as described in Section 7.7 and will be coded to system organ class and preferred term according to MedDRA, Version 21.1 or later. A TEAE is defined as described in Section 7.1. The following AE summaries will be reported by system organ class, preferred term, and combined participant status and dementia type at baseline:

- TEAEs
- Treatment-related TEAEs
- TEAEs by relationship to study drug
- TEAEs by severity
- SAEs
- TEAEs leading to study drug discontinuation
- TEAEs leading to study discontinuation

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. A separate analysis of AEs identified through MRI will not be conducted.

8.4.2.5. Physical and Neurological Examinations

Separate shift tables for physical and neurological examinations will be generated by the categorical interpretation of findings and will be presented by body system.

8.4.2.6. Vital Signs Analysis

Actual values and changes from baseline for vital signs and weight will be summarized at each time point using descriptive statistics.

8.4.2.7. Electrocardiogram Analysis

Actual values and changes from baseline for quantitative ECG results will be summarized at each time point using descriptive statistics. A shift table will be generated for the categorical interpretation of ECGs. Any grade 3 or higher QTcF prolongation will be listed.

8.4.2.8. Clinical Laboratory Analysis

Actual values and changes from baseline for clinical laboratory test results will be summarized at each time point using descriptive statistics. Shift tables will be generated for clinical laboratory test results.

8.4.2.9. Sheehan Suicidality Tracking Scale

A summary table for Sheehan-STS Total Score will be presented by time point using descriptive statistics.

8.4.2.10. Immunogenicity Analysis

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

8.4.3. Analysis of Pharmacokinetic and Pharmacodynamic Biomarker Endpoints

8.4.3.1. Analysis of Secondary Pharmacokinetic Endpoints

All PK summaries will be presented using the PK analysis population.

Individual and mean serum AL001 concentration-time data will be tabulated and plotted by study day and mutation carriers. As applicable, the serum PK of AL001 will be summarized by estimation of maximum observed concentration (C_{max}), trough concentration (C_{trough}), and area under the concentration-time curve (AUC_{ss}) on the basis of results obtained following multiple doses of AL001 by study day and cohort.

The individual serum concentration versus actual time data for AL001 will be used to derive PK parameters by standard noncompartmental methods using Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey, USA) Version 6.4 or higher. The individual PK parameters will be presented in listings. PK parameters will be summarized in tables using the following descriptive statistics: n, arithmetic mean, SD, coefficient of variation (CV), geometric mean, geometric mean CV, minimum, median, and maximum. Geometric mean and geometric mean, 90% CI, and CV will only be included for C_{max}, C_{trough}, and AUC_{ss} (if data permit).

Potential correlations of relevant PK parameters with demographics, safety (including QT changes), and PD 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.

8.4.3.2. Analysis of Secondary and Exploratory Pharmacodynamic Endpoints

All PD summaries will be presented using the PD analysis population.

PD endpoints will be described and summarized by study day and mutation carriers at baseline and each time point specified in the Schedules of Assessments (Table 4, Table 5, Table 6, Table 7,Table 8, and Table 9), as will the percent change from baseline for each PD endpoint. Pharmacodynamic endpoints to be evaluated in plasma and CSF samples will include but are not limited to PGRN, Sortilin, and NfL.

Summary statistics for PD endpoints and their corresponding changes from baseline (e.g., percent change from baseline) will be tabulated by study day and cohort. The time course of PD endpoints will be presented graphically for both observed values and percent change from baseline values. In addition, a mixed model of repeated measures (MMRM) may be used to summarize the mean percent changes in PD endpoints from baseline with 95% CIs. Association between PD endpoints and clinical response may also be explored.

The PK-PD relationship may be modeled by population PK/PD model using nonlinear mixed effects modeling. Baseline exploratory PD biomarkers may also be explored as potential

predictors of response to AL001, including baseline serum or CSF PGRN levels and *GRN* or *C9orf72* genotyping.

8.4.3.3. Analyses of Exploratory Pharmacodynamic Biomarker Endpoints

All exploratory PD biomarker summaries will be presented using the PD biomarker population.

Correlations among fluid PD biomarker levels, imaging PD measures, and clinical outcome measures will be evaluated, and details will be provided in the SAP.

8.4.3.3.1. Magnetic Resonance Imaging

Actual results and percent change from baseline values for quantitative MRI parameters will be summarized by visit using descriptive statistics. Mean percent change from baseline values, plus or minus the SD, will also be presented in a plot.

8.4.3.3.2. Other Exploratory Pharmacodynamic Biomarkers

Actual results and change from baseline values for other exploratory PD biomarker parameters will be summarized by visit using descriptive statistics. Mean change from baseline values, plus or minus the SD, will also be presented in a plot.

8.4.4. Analyses of Exploratory Clinical Outcome Assessment Endpoints

All COA summaries will be presented using the safety population. The full details of analysis for COA will include total and subscale scores and will be provided in the SAP.

Actual results and change from baseline values for COA total and/or subscale scores will be summarized by visit using descriptive statistics. Mean change from baseline values, plus or minus the SD, will also be presented in a plot.

The COA endpoint will be assessed using MMRM methodology. The dependent variable will be the change from baseline score to each postbaseline visit assessment. The fixed effects will include the participant mutation type, and time point will be the repeated measure. Covariates including but not limited to baseline PGRN level, sex, and age may be explored.

8.4.5. Interim Analyses

An iDMC will review safety data during the course of the study to provide recommendations to Alector on study conduct. The details of the iDMC are provided in Section 12.1 and in a separate charter.

9. DATA QUALITY ASSURANCE

This study will be conducted according to the 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 standard operating procedures. 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 investigational site personnel. Electronic case report forms (CRFs) and electronic data capture will be utilized. The electronic data capture (EDC) system is validated and compliant with local regulatory requirements. 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 will maintain adequate case histories for the participants treated as part of the research under this protocol. The investigator will 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 some COAs, whereas others will be performed on paper and entered into the eCRF. This will be part of the source.

A separate device will be used for the WLAs (optional; UK, US, or Canadian participants only). All data collected by the Winterlight application will be stored securely on the device and queued for upload to Winterlight's secure servers.

The investigator will adhere to Good Documentation Practice, and investigative site personnel will enter participant data into the eCRF. The analysis datasets will be a combination of these data and data from other sources (e.g., 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, e.g., removing errors and inconsistencies in the data. Adverse Event terms will be coded using the MedDRA Version 21.1 or later and an internal validated medical dictionary, and concomitant medications will be coded using the WHO-DD, March 2019 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.

10. ETHICS

10.1. Independent Ethics Committee or Institutional Review Board

Local regulation 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 site and will be available for review by Alector (or designee).

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 (or designee), 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 informed consent in compliance with US Title 21 CFR (Part 50) and applicable regulatory authority regulations shall be obtained from each participant before enrolling in the Part 1 treatment period of the study, before continuation of treatment in the optional Part 2, or before performing any unusual or nonroutine procedure that involves risk to the participant. An informed consent template may be provided by Alector to investigational sites. If any site-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by Alector (or designee) or both before IRB/IEC submission. Once reviewed, the consent 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 participating participants must sign the revised form.

Before recruitment and enrollment into Part 1 and Part 2, each prospective participant and 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 participant understands the implications of participating in the study, the participant will be asked to give consent to participate in the study by signing the ICF. The participant's study partner will also be asked to give consent to participate in the study by signing an ICF.

If the study participant is not competent, a legally authorized representative must provide informed consent on their behalf, and the participant must provide assent, in accordance with the local regulations, guidelines, and 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, in accordance with the local regulations, guidelines, and the IRB/IEC.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the participant, legally authorized representative, or 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 standard operating procedures 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 6.5.4, participants will provide informed consent in accordance with the standard operating procedures of the investigational sites.

Consent for Optional WLA Assessments (optional, US, UK, and Canadian participants only)

Prior to participating in the optional WLAs, participants and study partners will provide informed consent in accordance with the standard operating procedures 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 standard operating procedures, 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. Clinical information will not be released without the written permission of the participant (or the participant's legally authorized representative), except as necessary for monitoring and auditing by Alector, its designee, the FDA/European Medicines Agency (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 (or designee) must be obtained for the disclosure of any said confidential information to other parties.

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 (or designee) 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 (or designee) 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 sub-investigator 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 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 site for this study, in accordance with 42 CFR 493.

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 registers before enrollment of participants begins.

11.5. Adherence to 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 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 (or designee) should be notified if the investigator becomes aware of any SAE that is believed to be related to prior study drug.

11.7. Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and Alector and regulatory authority(ies) 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 at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. 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 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 may 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 such issues.

Data 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. Independent Data Monitoring Committee (iDMC)

An iDMC will review Part 1 safety data during the course of Part 1 of the study to provide recommendations to Alector on study conduct. The iDMC will be comprised of two physicians (including one with disease area expertise) and a statistician, each of which are independent from the Sponsor. Data reviews will be conducted after the first 6 participants complete approximately 12 weeks of study drug, and then every 6 months thereafter until the last participant completes Part 1 the study. The details of the iDMC are provided in a separate charter.

12.2. 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 letter 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 personnel.

All aspects of the study will be carefully monitored, by Alector or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

12.3. 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 should promptly notify Alector (or designee) of any audits scheduled by any regulatory authorities. Dependent upon the scope of the regulatory authority audit, Alector may elect to assist the site in preparation or support. The investigation should promptly forward copies of any audit reports received to Alector.

12.4. Management of Protocol Amendments and Deviations

12.4.1. 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 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.

12.4.2. 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 should 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 the ones that affect the participants' safety or the study endpoints. 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.

12.5. Study Termination

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

The end of the study is defined as the date on which the last participant completes the last visit (includes Safety Follow-up visit).

12.6. Final Report

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

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 registers.

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14. APPENDICES

APPENDIX 1. SCHEDULES OF ASSESSMENTS

Table 4: Schedule of Assessments for Part 1, Treatment Period (Through Week 53)

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

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

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

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

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

[c] A complete neurological examination will be performed at screening, Week 25, Week 49, Week 73, Week 97 and at EOT/EOS/Safety Follow-up, and includes the evaluation of consciousness, orientation, cranial nerves, motor and sensory system, coordination and gait, and reflexes. Limited or symptom-directed examinations are required at all other specified time points, prior to study drug administration (if applicable). A limited examination or symptom-

directed examination should focus on the organ system or affected body area. Record abnormalities observed at screening on the General Medical History and Baseline Conditions page of the eCRF. At subsequent visits, record new or worsened clinically significant abnormalities as AEs on the AE eCRF.

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

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

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

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

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

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

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

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

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

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

[n] During study drug treatment, magnetic resonance imaging to be performed within ±7 days of a treatment visit. *GRN* mutation carriers previously treated in Study AL001-1 may not be required to repeat the imaging screening assessment if it has been performed within 3 months prior to screening.

[o] A diagnostic characterization form will be completed in an electronic data capture system at screening, week 97, and EOT/EOS for symptomatic participants only. It will also be completed for any asymptomatic participant who becomes symptomatic during the course of the study; for these participants, the diagnostic characterization form will be completed only at the first visit in which they exhibit clinical symptomatology.

[p] The COAs consist of the Clinical Dementia Rating Scale plus behavior and language domains from the National Alzheimer's Disease Coordinating Center Frontotemporal Lobar Degeneration module, Frontotemporal Dementia Rating Scale, Clinical Global Impression of Improvement, Clinical Global Impression of Severity, Color Trails Test Part 2, and the Repeatable Battery for the Assessment of Neuropsychological Status. The Clinical Global Impression of Improvement is not administered at baseline. Neurocognitive and functional tests will be performed prior to study drug administration (if applicable) and prior to any stressful procedures (e.g., blood collections, imaging).

[q] Winterlight Labs Speech Assessments (WLA) (for US, UK, and Canadian participants who agree to participate in the optional assessments only) will be conducted at home. Participants will have the option to complete the WLA after assessment visits only (WLA-A), after treatment visits only (WLA-B) or both (WLA-A and WLA-B). Assessments are conducted at home within ±7 days of the visit and will be supervised by the study partner. The study partner will be asked to complete a questionnaire online within ±7 days of the EOS visit.

[r] All AEs and SAEs must be recorded and reported, regardless of cause or relationship, that occur after the participant signs informed consent and through the Part1/Part 2 EOS or Safety Follow-up visit, whichever is later. Any unresolved AEs and SAEs will be followed up through satisfactory clinical resolution. Additionally, SAEs considered related to study drug which occur at any time during the study will be reported by the investigator regardless of the AE/SAE collection window. At every study visit, participants will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (prescription drugs, herbal products, vitamins, minerals, vaccines, topical medications, and over-the-counter medications). Review of AEs and concomitant medications will be performed before and after study drug administration (when applicable).

Table 5: Schedule of Assessments for Part 1, Treatment Period (Through Week 97)

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

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

[a] Visit 17A should occur the following day after Visit 17.

[b] A Safety Follow-up visit will be performed 10 weeks following the last dose of AL001. The Safety Follow-up visit may be substituted by a scheduled visit if it occurs within the same window.

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

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

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

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

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

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

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

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

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

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

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

[n] During study drug treatment, magnetic resonance imaging to be performed within ±7 days of a treatment visit. *GRN* mutation carriers previously treated in Study AL001-1 may not be required to repeat the imaging screening assessment if it has been performed within 3 months prior to screening.

[o] A diagnostic characterization form will be completed in an electronic data capture system at screening, week 97, and EOT/EOS for symptomatic participants only. It will also be completed for any asymptomatic participant who becomes symptomatic during the course of the study; for these participants, the diagnostic characterization form will be completed only at the first visit in which they exhibit clinical symptomatology.

[p] The COAs consist of the Clinical Dementia Rating Scale plus behavior and language domains from the National Alzheimer's Disease Coordinating Center Frontotemporal Lobar Degeneration module, Frontotemporal Dementia Rating Scale, Clinical Global Impression of Improvement, Clinical Global Impression of Severity, Color Trails Test Part 2, and the Repeatable Battery for the Assessment of Neuropsychological Status. The Clinical Global Impression of Improvement is not administered at baseline. Neurocognitive and functional tests will be performed prior to study drug administration (if applicable) and prior to any stressful procedures (e.g., blood collections, imaging).

[q] Winterlight Labs Speech Assessments (WLA) (for US, UK, and Canadian participants who agree to participate in the optional assessments only) will be conducted at home. Participants will have the option to complete the WLA after assessment visits only (WLA-A), after treatment visits only (WLA-B) or both (WLA-A and WLA-B). Assessments are conducted at home within +/- 7 days of the visit and will be supervised by the study partner. The study partner will be asked to complete a questionnaire online within +/- 7 days of the Study Completion visit.

[r] All AEs and SAEs must be recorded and reported, regardless of cause or relationship, that occur after the participant signs informed consent and through the Part 1/Part 2 EOS or Safety Follow-up visit, whichever is later. Any unresolved AEs and SAEs will be followed up through satisfactory clinical resolution. Additionally, SAEs considered related to study drug which occur at any time during the study will be reported by the investigator regardless of the AE/SAE collection window. At every study visit, participants will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (prescription drugs, herbal products, vitamins, minerals, vaccines, topical medications, and over-the-counter medications). Review of AEs and concomitant medications will be performed before and after study drug administration (when applicable).

[s] Participants who complete the Part 1 96-week treatment period (Week 97), who provide informed consent to participate in Part 2 (optional OLE) and meet all the eligibility criteria for the Part 2 OLE (prior to Week 101 study drug administration), will complete the Week 97 visit and continue to Part 2 (Week 101) to receive their next regularly scheduled dose of AL001 according to the OLE administration schedule (continuation from Week 97 to Week 101). All other participants who complete the Part 1 96-week treatment period and who do not continue in Part 2 will complete a Part 1 EOS visit at the scheduled Week 97 timepoint. A Safety Follow-up visit will be performed 10-weeks after their last study drug administration (Week 107, +/- 7 days).

[t] A Part 1 EOT visit will be completed by participants who discontinue study drug but remain in the study and continue to perform assessments. Part 1 EOT assessments should be completed as soon as possible after the decision is made. A Part 1 EOS visit will be completed by participants who discontinue study drug and all assessments. Part 1 EOS assessments should be completed as soon as possible after the decision is made.

Table 6: Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarker Sample and Imaging Assessments – Part 1, Treatment Period

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

Timepoint	Vital Signs	Serum PK sample [a]	Triplicate ECG	Serum ADA sample	Progranulin plasma sample	Exploratory plasma PD biomarker samples [b]	Whole blood for WBC	Exploratory whole blood PD biomarker samples [c]
V15 (Week 53): End of infusion	x	x						
V16 (Week 57): Pre-dose	x							
V16 (Week 57): End of infusion	x							
V17 (Week 61): Pre-dose	x	x		x	x	x	x	x
V17 (Week 61): End of infusion	x	x						
V17 (Week 61): 3 hr ± 90 minutes post end of infusion		x						
V17A (Week 61): The next day after V17		x			x			
V18 (Week 65): Pre-dose	x							
V18 (Week 65): End of infusion	x							
V19(Week 69): Pre-dose	x							
V19 (Week 69): End of infusion	x							
V20 (Week 73): Pre-dose	x	x	x	x	x	x	x	x
V20 (Week 73): End of infusion	x	x	x					
V21 (Week 77): Pre-dose	x							
V21 (Week 77): End of infusion	x							
V22 (Week 81): Pre-dose	x							
V22 (Week 81): End of infusion	x							
V23 (Week 85): Pre-dose	x	x		x	x	x	x	x
V23 (Week 85): End of infusion	x	x						
V24 (Week 89): Pre-dose	x							
V24 (Week 89): End of infusion	x							
V25 (Week 93): Pre-dose	x							
V25 (Week 93): End of infusion	x							
V26 (Week 97): Pre-dose	x	x	x	x	x	x	x	x
V26 (Week 97): End of infusion	x	x	x					
Safety Follow-up)	x	x	x	x	x			
Part 1 EOT/EOS	x	x	x	x	x	x	x	x

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

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

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

[c] Exploratory whole blood biomarkers include mRNA and other analytes.

Table 7: Schedule of Assessments for Part 2 (Optional OLE) (Through Week 161)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[n] Winterlight Labs Speech Assessments (WLA) (for US, UK, and Canadian participants who agree to participate in the optional assessments only) will be conducted at home. Participants will have the option to complete the WLA after assessment visits only (WLA-A), after treatment visits only (WLA-B) or both (WLA-A and WLA-B). Assessments are conducted at home within ±7 days of the visit and will be supervised by the study partner. The study partner will be asked to complete a questionnaire online within ±7 days of the EOS visit.

[o] All AEs and SAEs must be recorded and reported, regardless of cause or relationship, that occur after the participant signs informed consent and through the Part1/Part2 EOS or Safety Follow-up visit, whichever is later. Any unresolved AEs and SAEs will be followed up through satisfactory clinical resolution. Additionally, SAEs considered related to study drug which occur at any time during the study will be reported by the investigator regardless of the AE/SAE collection window. At every study visit, participants will be asked a standard non-leading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (prescription drugs, herbal products, vitamins, minerals, vaccines, topical medications, and over-the-counter medications). Review of AEs and concomitant medications will be performed before and after study drug administration (when applicable).

Table 8: Schedule of Assessments for Part 2 (Optional OLE) (Through Week 197)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[m] Winterlight Labs Speech Assessments (WLA) (for US, UK, and Canadian participants who agree to participate in the optional assessments only) will be conducted at home. Participants will have the option to complete the WLA after assessment visits only (WLA-A), after treatment visits only (WLA-B) or both (WLA-A and WLA-B). Assessments are conducted at home within ±7 days of the visit and will be supervised by the study partner. The study partner will be asked to complete a questionnaire online within ±7 days of the EOS visit.

[n] All AEs and SAEs must be recorded and reported, regardless of cause or relationship, that occur after the participant signs informed consent and through the Part1/Part2 EOS or Safety Follow-up visit, whichever is later. Any unresolved AEs and SAEs will be followed up through satisfactory clinical resolution. Additionally, SAEs considered related to study drug which occur at any time during the study will be reported by the investigator regardless of the AE/SAE collection window. At every study visit, participants will be asked a standard non-leading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (prescription drugs, herbal products, vitamins, minerals, vaccines, topical medications, and over-the-counter medications). Review of AEs and concomitant medications will be performed before and after study drug administration (when applicable).

[o] At Week 197, participants who complete the Part 2 96-week OLE period will complete a Part 2 EOS visit at the scheduled Week 197 timepoint. Participants who complete Visit 51/Week 197 will return for a Safety Follow-up visit 10 weeks after their last AL001 administration (Week 207, +/- 7 days).

[P] Participants who discontinue study drug and/or all assessments prior to completing the 96-week Part 2 treatment period will complete a Part 2 EOS visit as soon as possible after the decision is made.

[q] A Safety Follow-up visit will be performed 10 weeks following the last dose of AL001. The Safety Follow-up visit may be substituted by a scheduled visit if it occurs within the same window.

Table 9: Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarker Sample and Imaging Assessments – Part 2 (Optional OLE)

Timepoint	Vital Signs	Serum PK sample [a]	Triplicate ECG	Serum ADA sample	Progranulin plasma sample	Exploratory plasma PD biomarker samples [b]
V27 (Week 101): Pre-dose	x					
V27 (Week 101): End of infusion	x					
V28 (Week 105): Pre-dose	x					
V28 (Week 105): End of infusion	x					
V29 (Week 109): Pre-dose	x					
V29 (Week 109): End of infusion	x					
V30 (Week 113): Pre-dose	x					
V30 (Week 113): End of infusion	x					
V31 (Week 117): Pre-dose	x					
V31 (Week 117): End of infusion	x					
V32 (Week 121): Pre-dose	x	x	x	x	x	x
V32 (Week 121): End of infusion	x	x	x	x	x	x
V33 (Week 125): Pre-dose	x					
V33 (Week 125): End of infusion	x					
V34 (Week 129): Pre-dose	x					
V34 (Week 129): End of infusion	x					
V35 (Week 133): Pre-dose	x					
V35 (Week 133): End of infusion	x					
V36 (Week 137): Pre-dose	x					
V36 (Week 137): End of infusion	x					
V37 (Week 141): Pre-dose	x					
V37 (Week 141): End of infusion	x					
V38 (Week 145): Pre-dose	x	x	x	x	x	x
V38 (Week 145): End of infusion	x	x	x	x	x	x
V39 (Week 149): Pre-dose	x					
V39 (Week 149): End of infusion	x					
V40 (Week 153): Pre-dose	x					
V40 (Week 153): End of infusion	x					
V41 (Week 157): Pre-dose	x					

Timepoint	Vital Signs	Serum PK sample [a]	Triplicate ECG	Serum ADA sample	Progranulin plasma sample	Exploratory plasma PD biomarker samples [b]
V41 (Week 157): End of infusion	x					
V42 (Week 161): Pre-dose	x					
V42 (Week 161): End of infusion	x					
V43 (Week 165): Pre-dose	x					
V43 (Week 165): End of infusion	x					
V44 (Week 169): Pre-dose	x	x	x	x	x	x
V44 (Week 169): End of infusion	x	x	x	x	x	x
V45 (Week 173): Pre-dose	x					
V45 (Week 173): End of infusion	x					
V46 (Week 177): Pre-dose	x					
V46 (Week 177): End of infusion	x					
V47 (Week 181): Pre-dose	x					
V47 (Week 181): End of infusion	x					
V48 (Week 185): Pre-dose	x					
V48 (Week 185): End of infusion	x					
V49 (Week 189): Pre-dose	x					
V49 (Week 189): End of infusion	x					
V50 (Week 193): Pre-dose	x					
V50 (Week 193): End of infusion	x					
V51 (Week 197): Pre-dose	x	x	x	x	x	x
V51 (Week 197): End of infusion	x	x	x	x	x	x
Safety Follow-up	x	x	x	x	x	
Part 2: EOS	x	x	x	x	x	x

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

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

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

APPENDIX 2. CLINICAL OUTCOME ASSESSMENTS – NEUROCOGNITIVE AND FUNCTIONAL TESTS

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 assessment is the CDR® plus the Frontotemporal Dementia Behavior and Language Domain scores from the NACC FTLD module. Data for this scale will be captured through completion of the standard CDR and a domain-specific container form labeled Frontotemporal Dementia Behavior and Language Domains (FTD-BLD). The necessary information to rate these domains is obtained through a semi-structured interview of the participant and a reliable informant or collateral source (e.g., a caregiver).

Clinical Dementia Rating Scale (CDR®):

Washington University's CDR is a global assessment instrument that yields global scores (CDR-GS). The sum of boxes (CDR-SB) 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 (e.g., a caregiver).

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.

Clinical Global Impression of 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 of 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.

Color Trails Test (CTT):

The CTT is a language-free version of the Trail Making Test that was developed to allow for broader cross-cultural assessment of sustained attention and divided attention in adults. In the CTT, numbered circles are printed with vivid pink or yellow backgrounds. For Part 1, the respondent uses a pencil to rapidly connect circles numbered 1 to 25 in sequence. For Part 2, the respondent rapidly connects numbered circles in sequence, but alternates between pink and yellow. The length of time to complete each study is recorded. Part 2 of the CTT will only be assessed in this study.

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.

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 US, UK, and Canadian participants who are proficient in English 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 (Appendix 1).

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 (e.g., 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 a tablet 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.

Participants will have the option to complete the WLA after assessment visits only (WLA-A), after treatment visits only (WLA-B) or both (WLA-A and WLA-B). These assessments are conducted at home within ±7 days of a treatment assessment visit. Assessments will be supervised by the study partner.

APPENDIX 3. ADAPTATION OF TRIAL PROTOCOL DURING COVID-19 PANDEMIC

Background

The COVID-19 pandemic has caused significant disruption globally and is a public health emergency that has an impact on the conduct of global clinical research activities. The safety of patients and site staff continues to be paramount, and Alector has made the decision to continue patient participation in the AL001-2 study at the discretion of the investigator, and in accordance with each site's regional or country health authority guidelines and recommendations regarding the COVID-19 pandemic.

Alector, in collaboration with the clinical research organization (CRO), is committed to performing pandemic-related risk reviews of study procedures and mitigating the effect of the pandemic on the conduct of this study. These ongoing collaborative risk reviews include analysis of COVID-19 restrictions as they impact patient safety, study, and data integrity, and the impact on program timelines continues to be assessed. The review has been and will continue to be conducted regularly and will take into consideration any new information regarding the pandemic, including continuous assessment of adverse events reported in the study.

Implementation of COVID-19 Appendix

The implementation of adaptations to study visits and procedures detailed described in this appendix applies only to the exceptional circumstances of the COVID-19 pandemic. Procedure adaptations apply to those sites that have been impacted by the pandemic through restrictions to movement/trave, study site restrictions, and where the safety of the patient may be adversely impacted by on-site visits.

The implementation of these adaptations will be determined on a site-by-site basis dependent on local requirements, and will be reviewed on a regular basis with Alector to confirm the continued need for implementation.

Essential On-Site Assessments and Remote Visits (Via Phone or Video)

Continuation of the study during the pandemic does, and will continue, to impact the ability of some sites to conduct all protocol assessments per the Schedules of Events detailed in Appendix 1). This is due to reduced time for on-site visits, limited or no availability of some services at site, or the need to conduct visits remotely via telephone or via televisit (if approved locally).

The primary objective with any change to the study schedule is to ensure ongoing monitoring of patient safety.

On-site Essential Assessments

Where possible, all protocol assessments and treatments should be completed.

To accommodate reduced time on-site during study visits, the following reduced assessments schedule should be completed **as a minimum**:

- Vital signs, weight, physical, and neurological examinations
- Phlebotomy and urinalysis, including pregnancy test
- ECGs
- Collection of AEs and concomitant medications
- Sheehan-STS
- Study drug administration

Remote Essential Assessments

If participants or raters 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
- The following Clinical Outcome Assessments (COAs) listed below can be completed remotely:

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 (i.e. phone or video conferencing) administration, remote administration by phone has been validated for 6 of the domains (Randolph, C., et al, TELEPHONE ADMINISTRATION OF THE CDR: EXCELLENT AGREEMENT WITH FACE-TO-FACE ADMINISTRATION, 2014). Scoring anchors can be reliably differentiated for the remaining CDR® plus NACC FTLD two domains (language and behavior) via phone, however video conferencing would yield more reliable data for scoring these domains and eliminate the need to rely on the caregiver for observations (e.g., the rater can evaluate subject appearance, facial expression, and 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, subject, and caregiver are not in the same room.

- In the circumstance that the primary rater is remote, and the subject and back-up 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 phone. The back-up rater should observe the subject while they are answering the questions, and then provide observations of the subject behavior to the primary rater. Missing data from direct observation, which cannot be provided by the primary rater, can be completed by the back-up rater, as long as they are appropriately trained on the scale. Final observational assessments should be made by the primary rater.

2. **Frontotemporal Dementia Rating Scale (FRS)**

   - **Recommendation:** As a clinician-administered interview with the study partner, the FRS 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 subject and back-up 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 FRS questions over the phone. The back-up rater should observe the subject while they are answering the questions, and then provide observations of the subject behavior to the primary rater. Missing data from direct observation, which cannot be provided by the primary rater, can be completed by the back-up rater, as long as they are appropriately trained on the scale. Final observational assessments should be made by the primary rater.

3. **CGI**

   - **Recommendation:** A general, unstructured evaluation, discussion with an informant, as well as 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. Since the CGI is scored based on the CDR® plus NACC FTLD interview, a separate interview is not required.

4. **Sheehan-STS**

   - **Recommendation:** This can be completed via phone. Per Dr. Sheehan, a copy of scale should be provided for the subject to view when they are being evaluated.

Please note that some scales requiring subject performance, like drawing or writing, are not validated for remote administration and **may not be administered via telephone** (e.g., Color Trails Test [CTT] and Repeatable Battery for the Assessment of Neuropsychological Status [RBANS]).

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

Scale	Communication Technologies
CDR® plus NACC FTLD	Video Conference (Please note that a phone assessment might be done, however, the Language domain impairment should be taken into account and this should be approved by Alector)
CGI-I	NA
CGI-S	NA
FRS	Phone
Sheehan-STS	Phone
RBANS	Should **not** be administered remotely
CTT	Should **not** be administered remotely

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

- 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.
- Ensure that scale administration guidelines indicated in the scale manual and tutorial are carefully followed when adapted for use via telephone.
- 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 (e.g., 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 (e.g., a telephone with speakerphone).
- Always use the speaker phone for the scales that should be recorded for Independent Review.
- Scales should be administered as if informant and/or subject were face-to-face with the rater and should be administered in a quiet, distraction-free interview environment.
- There may be situations in which study partners or raters are remote. In these cases, the following guidance should be followed:
  - If the study partner/caregiver is remote and the subject is on-site, scales can be administered per procedure, with study partner/caregiver providing answers to the site rater.
  - If the primary rater is remote, and the subject and back-up rater are on-site, scales can still be administered by the primary rater. The back-up 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 Frontotemporal Dementia Rating Scale (FRS) sections.

On-site Assessments Unable to be Completed at Scheduled Visits

In the event that a scheduled assessment is unable to be completed at site, e.g., limited availability/restriction of equipment (e.g., MRI), patient limited time on-site or because a remote visit was completed, the missed assessments may be completed at a future on-site visit as determined and approved by the medical monitor.

The approval of the medical monitor must be obtained prior to completion of these moved assessments.

COVID-19 Reporting

In the event where a study subject is diagnosed with COVID-19 infection, the local health authority recommendations regarding treatment should be followed and the event should be reported as an AE/SAE depending on the severity of infection and diagnosis. Refer to Section 7 of the protocol.

Remote Consent

Where it is allowed by country/site regulations, a remote eConsent will be provided that allows a patient to be remote from the site and participate in the consent process.

Remote Source Document Verification

Remote source document verification will be employed **only** in the following circumstance:

- National law, Regulatory Authorities and IRB/Ethics Committee permit this process and approval is obtained.
- On-site clinical research associate (CRA) visits are not permitted due to continued COVID-19 restrictions.
- There is a need to complete source document verification for the following reasons:
  - Study Data assessment review of critical study milestones (e.g., database lock)
  - Patient safety
  - A significant backlog of data monitoring that could impact data integrity or patient safety.

Prior to commencing remote source document verification, the following documentation must be completed:

- The Site CRA will complete a confidentiality agreement committing to securely destroy any copies of documents received from sites (paper or electronic), nor take any recording during video access.

- Remote source data verification (SDV) will only be completed for subjects who have consented to allow access to their health records remotely.

At Home Study Drug Administration

In most instances, study drug should be administered at the investigational site. In the event the participant is unable to have study drug administered at the investigational site (i.e., due to participant or site restrictions related to Covid-19) study drug administration for the third and subsequent infusions may be performed "at home" (i.e., at the participant's home or other suitable location) by a home healthcare provider who has appropriate training and expertise in IV administration. Study drug administration for the first and second infusion must be conducted at the investigational site, at home study drug administration for subsequent infusions may only be performed with Medical Monitor approval.

The following procedures must be performed for each at home study drug administration:

Before study drug administration:

- Home healthcare provider will record vital signs, including systolic and diastolic BP, pulse, body temperature, and respiratory rate (recorded after the participant has been resting for at least 5 minutes in the supine position)
- Home healthcare provider will conduct anassessment[1,2] to include evaluation of general appearance, skin, EENT, head and neck, extremities, abdomen, and respiratory, cardiovascular, neurological, and musculoskeletal systems
- Home healthcare provider will conduct a review of concomitant medication(s)
- Home healthcare provider will record any AEs (signs and symptoms) which may have occurred since previous visit
- Home healthcare provider will contact the investigative site by phone or video (investigator or designee) to review findings from the assessment, adverse events and concomitant medications
- Home healthcare provider must receive email confirmation from the investigative site to proceed with study drug administration, prior to initiating study drug administration.

During study drug administration:

- Approximately 15 and 45 minutes after initiating study drug administration, monitor vital signs, including systolic and diastolic BP, pulse, body temperature, and respiratory rate[2]
- Monitor for infusion-related reactions or injection-related reactions[3]
- Record any AEs (signs and symptoms)

After study drug administration

- Record vital signs, including systolic and diastolic BP, pulse, body temperature, and respiratory rate (recorded within 15 minutes after the end of infusion)
- Monitor for infusion-related reactions or injection-related reactions for at least 90 minutes post-infusion[3]
- Conduct an assessment[1,2] to include evaluation of general appearance, skin, EENT, head and neck, extremities, abdomen, and respiratory, cardiovascular, neurological, and musculoskeletal systems
- Record any AEs (signs and symptoms)

If any AEs are observed during or after study drug administration the home healthcare provider must contact the clinical site by phone or video (investigator or designee) to review findings and to take appropriate action(s), if directed by the investigator (or designee).

If required, the site investigator may also conduct a tele visit prior to, during, or after study drug administration.

[1] The assessment will substitute for the protocol specified physical and neurological examination .
[2] Abnormalities identified during the assessment should be recorded as an AE and reported to the site in order to be entered in the EDC.
[3] Management of infusion-related and/or injection-related reactions is described in Protocol Section 5.1.2.