CLINICAL STUDY PROTOCOL

AL001-ALS-201

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AL001 in *C9orf72*-Associated Amyotrophic Lateral Sclerosis

Investigational Product:	AL001, human recombinant anti-human sortilin IgG1 monoclonal antibody
Indication:	*C9orf72*-Associated Amyotrophic Lateral Sclerosis (C9ALS)
Study Phase:	2
IND Number:	154279
Sponsor:	Alector, Inc. 131 Oyster Point Boulevard, Suite 600 South San Francisco, CA 94080, US Telephone: +1 650-837-0384
Vice President, Clinical Development:	Daniel Maslyar, MD [redacted]
Medical Monitor:	Margherita Torti, MD [redacted]
Protocol Version and Date:	Version 3.0, 11 February 2022 Version 2.0, 21 April 2021 Version 1.0, 18 December 2020

CONFIDENTIAL

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PROTOCOL APPROVAL – SPONSOR SIGNATORY

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Protocol Version and Date: Version 3.0, 11 February 2022

The undersigned accept the content of this protocol in accordance with the appropriate regulations and agrees to adhere to it throughout the execution of the study.

See signature manifest at the end of the document

Daniel Maslyar, MD **Date**

[redacted]

Alector, Inc.

PROTOCOL APPROVAL – LEAD STATISTICIAN

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Brian Mangal, MS

[redacted]

Date

PRINCIPAL INVESTIGATOR PROTOCOL APPROVAL SIGNATURE PAGE

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DocuSigned by:
Sabrina Paganoni
Signer Name: Sabrina Paganoni
Signing Reason: I approve this document
Signing Time: 14-Feb-2022 | 10:36 PST
58705BF61CB842A887521BEB826294FA

Sabrina Paganoni, MD, PhD

[redacted]

SITE INVESTIGATOR AGREEMENT SIGNATURE PAGE

I have read and understood all sections of the protocol specified below and the accompanying Investigator's Brochure. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Alector with complete and timely information, as outlined in the protocol. I will not supply study treatment to any person not authorized to receive it. Subject identity will not be disclosed to third parties or appear in any study reports or publications. Study documents will be stored appropriately to ensure their confidentiality. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to supervise and abide by all described protocol procedures. I agree to comply with the International Council for Harmonisation (ICH) harmonized tripartite guideline E6(R2): Good Clinical Practice (GCP), applicable U.S. Food and Drug Administration (FDA) regulations and guidelines, including those identified in Title 21 CFR Parts 11, 50, 54, and 312, central Institutional Review Board (IRB) guidelines and policies, and the Health Insurance Portability and Accountability Act (HIPAA).

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

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Investigator Signature	
Date of Signature	
Printed Name and Title	
Site Number	
Site Name	
Site Address	

STATEMENT OF COMPLIANCE

This study will be conducted in compliance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements, including United States Code of Federal Regulations (CFR) Title 45 CFR Part 46 and Title 21 CFR Parts 50, 56, and 312.

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Version 2.0 of the protocol, dated 21 April 2021, has been revised. Typographical changes, formatting corrections, minor administrative changes, and minor text clarifications are not listed. The protocol synopsis has been revised according to the revisions noted below.

Important revisions are described below.

Figure 1: The footnote was corrected to state that "subjects who plan to discontinue the study early should be encouraged to return to the investigational site for an Early Termination visit, which is 8 weeks after the last dose of study treatment".

Synopsis: The text was updated to state that the trial will be conducted at approximately "10-16", instead of 10-12, Northeast ALS Consortium (NEALS) centers in the United States (US).

Synopsis and Section 1.3.2: Added text to clarify that AL001 is also known as latozinemab.

Section 1.2.3, Overview of Clinical Studies with AL001: The following text for Study AL001-1 was deleted "reduction of pro-inflammatory markers, increase in lysosomal proteins, and a trend in reduction of neurofilament light chain (NfL)" since subsequent data has revealed a trend for lysosomal proteins to decrease and NfL to be unchanged after treatment with AL001.

Section 1.2.3, Overview of Clinical Studies with AL001: The text was updated to reflect the number of subjects enrolled in Study AL001-2 as of 27 August 2021, and the most frequently report TEAEs in ongoing studies (AL001-1, AL001-2, AL001-3).

Section 1.3.2, Risks of AL001 and AL001-ALS-201 Study Procedures and Assessments: Interim safety results condensed for clarity.

Section 3.2, End of Study Definition: The text was corrected to state that "subjects who plan to discontinue the study early should be encouraged to return to the investigational site for an Early Termination Visit, which is 8 weeks after the last dose of study treatment".

Section 4.1, Inclusion Criteria:

- The text was revised to clarify the preferred method of measuring vital capacity is by slow vital capacity (SVC) unless forced vital capacity (FVC) is required due to pandemic-related restrictions.
- The text was updated to state that acceptable contraception for male subjects when having sexual intercourse with a female partner is defined as using a condom or having a vasectomy.
- The text was revised to clarify that "In the investigator's opinion", subjects must be able to complete all study procedures, including the IV study drug administration and lumbar punctures (LPs).

Section 4.3, Screening Failures: The text was revised to clarify that subjects who fail screening "may be allowed one rescreen following approval of Alector's Medical Monitor." The following text was deleted: "…there is no time restriction for rescreening".

Section 4.4, Strategies for Recruitment and Retention: The section was removed from the protocol.

Section 5.6.2.1, Blinded and Unblinded Personnel: Text was revised to state that "In addition to the iDMC and the independent statistical group supporting the iDMC, safety personnel, and the administrative pharmacy personnel will be unblinded as needed."

Section 5.7, Concomitant Therapy: Sentence was added to clarify that "Subjects who have not started riluzole or edavarone prior to the study will not be allowed to initiate these medications during study treatment given their potential to interfere with study endpoint assessments."

Section 5.8.1, Guidance for Management of Infusion-Related Reactions, Section 7.2.4, Anti-Drug Antibodies, and Appendix 1 Footnote #13 (previously #12): Text was revised to clarify that clinical laboratory samples should be drawn at the site "for central laboratory"; however, local laboratories may be utilized, and results assessed for safety by the investigator.

Section 6.1, Study Drug Discontinuation: Text was revised to clarify that subjects who "plan to" discontinue early from the study drug or study should complete an Early Termination Visit 8 weeks after the last dose of study treatment.

Section 6.2, Subject Withdrawal from the Study: Text was revised to state that all subjects who discontinue the study "during and after the treatment phase but before the final" scheduled Study Completion Visit should be encouraged to return to the investigational site for an Early Termination Visit 8 weeks after the last dose of study treatment.

Section 7.1.7 , Training and Validation: Deleted cross-reference to the Manual of Procedures (MOP).

Section 7.2, Biofluid Collection and Sample Retention: Revised cross-reference for instructions regarding the collection, processing, storage, and shipment of biosamples from the MOP to the central laboratory manual.

Section 7.2.2, Lumbar Puncture: Text was revised to clarify that "Subjects may only undergo a LP if they have a coagulation panel and platelet count performed (using a central or local laboratory) within 4 weeks prior to the LP. If the laboratory results are abnormal and warrant repeat studies, they should be repeated within a week prior to the LP, and can be repeated at a local laboratory as needed. Lumbar puncture at Visit 8 is to be performed prior to study drug administration, and at approximately the same time of the day as the Screening LP. The LP is to be performed after pulmonary function testing and administration of the ALSFRS-R. For subjects who are rescreened, if an LP was previously completed as part of Screening and it is within 12 weeks of reconsenting, then a repeat LP is not necessary."

Section 7.3.3, Clinical Safety Laboratory Test: Table 2 was revised to exclude "hepatitis B core antibody" as a serology test at Screening.

Section 7.3.5, Physical Examination: Text was revised to clarify that any new or worsened clinically significant abnormality does not need to be recorded on the AE eCRF if event is related to the patient's ALS disease progression.

Section 7.3.7, Columbia-Suicide Severity Rating Scale: Deleted cross-reference to the Manual of Procedures (MOP).

Section 8, Assessment of Safety: Clarified investigator responsibilities for reporting AEs/SAEs.

Section 8.1, Definition of Adverse Event: Revised list of items that an AE does not include by clarifying a previous condition as one that occurs "prior to signing informed consent", and

adding the following: "*Note:* Any serious procedural complication or hospital-emergent conditions (eg, nosocomial infection) would be reported as an SAE." Deleted item that says "The condition that led to the procedure may be an AE and must be reported."

Section 8.6.1, Eliciting and Documenting the Adverse Events: Revised text to clarify that abnormal laboratory test values or investigational findings reported as AEs or SAEs should be followed "until recovered/resolved, until stable, subject withdrawal of consent, lost to follow-up, or death, whichever comes first".

Section 8.6.3, Recording the Outcome and Follow-Up of Subjects Reporting an AE/SAE: Text was corrected for recording the outcome of an AE/SAE on the AE eCRF to be "recovered/resolved" instead of "recovered/resolved or attributable to other (defined) cause", or to be "not recovered/not resolved" instead of "not recovered/not resolving up to a 30-day follow-up period". No changes were made to other outcomes.

Section 8.7.1, Adverse Event and Serious Adverse Event Reporting: Revised the SAE information to be collected to add "all applicable seriousness criteria" and to delete "if applicable" for collecting seriousness of the SAE.

Section 8.8, Safety Monitoring: The following paragraph was moved from Section 9.3.6.1 to Section 8.8: "Safety will be continuously reviewed by a Medical Monitor in consultation with the study investigators. Adverse events will be reported to the Medical Monitor from the study EDC system at regular intervals throughout the study, and in real time when SAEs occur or when questions arise. The Medical Monitor will have the authority to recommend study discontinuation or modification based on medical concerns, including AE or SAE profiles."

Section 8.10.1, Special Situations: Text was revised to clarify that special situations (ie, non-standard medical conditions) provide valuable information about an investigational product and "therefore should be reported".

Section 10.1, Informed Consent Process: Text was revised to state that if the ICF is revised during the study, active participating subjects "may need to sign the revised consent form as determined by the IRB and/or Sponsor" instead of "must sign the revised consent form".

Section 10.6, Clinical Monitoring: Deleted cross-reference to the Manual of Procedures (MOP).

Section 10.6.1, Monitoring Report: Deleted cross-reference to the Manual of Procedures (MOP).

Section 10.7, Quality Assurance and Quality Control:

- Text was clarified to state that no "prospective protocol" waivers will be issued or approved/pre-approved for changes to the protocol. Deleted "or deviations".
- Text was revised to clarify that after "all subjects at the study site have completed the treatment phase of the study" instead of "at the end of the study site's participation" any unused investigational product will be destroyed in accordance with each institution's investigational product destruction policy, following the monitor's authorization of destruction.
- Text was revised to delete cross-reference to the MOP and added cross-reference to the "Pharmacy Manual", which contains a detailed description of investigational product storage, accountability, as well as resupply and destruction.

Section 10.9, Study Records Retention: Text was revised to delete statements that "The investigators should retain all study documents and records until they are notified in writing by the Sponsor or their representative." and "No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location."

Appendix 1, Schedule of Assessments:

- Coagulation was removed from Visit 4 (Week 8).
- LP was removed from Visit 5 (Week 12).

Appendix 1 Footnotes:

- Footnote #2 text was revised to add the following: If necessary, the Baseline Visit may be conducted over 2 consecutive days. The following procedures may be performed on the first day of the split visit: inclusion/exclusion review, weight, randomization, physical examination, neurological examination, ALSFRS-R, ALS-CBS, pulmonary function test, C-SSRS, and digital monitoring. The following must be completed on the second day of the split visit: collection of safety laboratory samples, serum PK samples (pre-infusion and post-infusion as outlined in footnote 11), biomarker samples, serum ADA samples, serum pregnancy test, vital signs, and 12-lead ECG. Study drug infusion must always be on the second day of a split Baseline Visit. Concomitant medication and AE review should be completed on each day."
- Footnote #3 was added as follows: "After the Baseline Visit, visit procedures at any subsequent visit may be completed over the course of a 48-hour period; however, the following must be completed on the day of study drug administration: collection of safety laboratory samples, serum PK samples (except for 24-hour post infusion PK at Visit 5, see footnote 11), biomarker samples, serum ADA samples, pregnancy test (if applicable), vital signs, and 12-lead ECG. The lumbar puncture must be performed prior to infusion for all visits where an LP is required (as outlined in footnote 15)."
- Footnotes #3 through #13 in Amendment 2.0 were renumbered to Footnotes #4 through #14 in Amendment 3.0.
- Footnote #10 (previously #9) was revised to remove the requirement to perform coagulation panel at Visit 4.
- Footnote #11 (previously #10) was revised to clarify serum PK samples drawn pre-infusion will be done "on the day of the infusion visit", and PK samples at Visit 5 will be collected at 3 hours (±90 minutes) and 24 hours (±6 hours) post end of infusion.
- Footnotes #14 and #15 were combined and revised as follows: "Subjects may only undergo a LP if they have a coagulation panel and platelet count performed (using a central or local laboratory) within 4 weeks prior to the LP. If the laboratory results are abnormal and warrant repeat studies, they should be repeated within a week prior to the LP, and can be repeated at a local laboratory as needed. Lumbar puncture at Visit 8 is to be performed prior to study drug administration, and at approximately the same time of the day as the Screening LP. The LP is to be performed after pulmonary function testing and administration of the ALSFRS-R. For subjects who are rescreened, if a LP was

previously completed as part of Screening and is within 12 weeks of reconsenting, then a repeat LP is not necessary."

- Footnote #17 was revised to clarify that timing of the home retest spirometry assessment with virtual coaching by study staff will be conducted 2 days "after" the Baseline visit.
- Footnote #19 was revised to clarify that C-SSRS "Baseline" Version will be completed at the "Baseline" visit, not at the Screening visit.
- Footnote #20 was revised to state that digital monitoring to occur "approximately weekly" instead of "with a visit window of ±3 days".
- Footnote #22 was deleted.
- Footnote #22 (previously #23) was updated to clarify that in the event of an infusion-related reaction, blood will be drawn for PK serum and ADA assessment of AL001 or placebo; the following laboratory tests should be drawn: CRP, ferritin, tryptase, and IL-6 (at 1 to 2 hours after the IRR, then again at 48-72 hours after the IRR). Where possible, clinical laboratory samples should be drawn at the site for the central laboratory; however, local laboratories may be utilized and results assessed for safety by the investigator.
- Footnote #24 was added: "Subjects may only undergo a LP if they have a coagulation panel and platelet count performed (using a central or local laboratory) within 4 weeks prior to the LP. If the laboratory results are abnormal and warrant repeat studies, they should be repeated within a week prior to the LP, and can be repeated at a local laboratory as needed. Lumbar puncture is to be performed at approximately the same time of the day as the Screening LP. The LP is to be performed after pulmonary function testing and administration of the ALSFRS-R."
- Footnote #25 was added: "The Early Termination Visit should occur 8 weeks after the last dose of study treatment."
- Previous Footnote #25 was renumbered to Footnote #26.

Appendix 2, Adaptation of Trial Protocol During the COVID-19 Pandemic: Added text that prior to commencing remote source document verification, the following documentation must be completed "if required per local regulations".

SYNOPSIS

Study Title	Study AL001-ALS-201: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AL001 in *C9orf72*-Associated Amyotrophic Lateral Sclerosis
Study Description	This is a phase 2 trial to test the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of AL001 in subjects with *C9orf72*-associated Amyotrophic Lateral Sclerosis (C9ALS). AL001 is hypothesized to protect motor neurons by increasing extracellular progranulin (PGRN) levels and thereby reducing TDP-43 pathology in amyotrophic lateral sclerosis (ALS). The trial has been designed to confirm elevation of progranulin (PGRN) and accumulation of AL001 in cerebrospinal fluid (CSF) and to provide proof-of-mechanism target engagement in preparation for a larger trial testing the clinical efficacy of AL001 in C9ALS.
Study Phase	Phase 2
Study Population	Approximately 45 subjects with C9ALS will be randomized in the study.
Study Sites and Coordinating (Principal) Investigator	The trial will be conducted at approximately 10-16 Northeast ALS Consortium (NEALS) centers in the United States (US). **Coordinating (Principal) Investigator** Sabrina Paganoni, MD, PhD Massachusetts General Hospital The Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital [redacted]
Investigational Product	AL001, a human recombinant anti-human sortilin immunoglobulin G (IgG)1 monoclonal antibody (also known as latozinemab) that selectively binds to sortilin to block the degradation of extracellular PGRN
Study Drug Administration	AL001 60 mg/kg or matching placebo will be administered intravenously (IV) every 4 weeks for 24 weeks.
Randomization and Stratification	Subjects will be randomly assigned to receive either standard of care + AL001 or standard of care + placebo (randomized 2:1) with stratification by rs5848 genotype (CC, CT, TT).
Objectives	Primary: • To evaluate the safety of AL001 in C9ALS • To evaluate the tolerability of AL001 in C9ALS • To evaluate AL001 PK parameters in serum and CSF • To evaluate plasma and CSF PGRN levels • To evaluate anti-drug antibodies (ADA) to AL001 in serum

	Secondary: • To evaluate the biological activity of AL001 as measured by neurofilament light chain (NfL) levels in the blood and CSF
	Exploratory: • To evaluate genotype-specific effects of AL001 on PD biomarkers for common variants of progranulin gene (*GRN*) • To evaluate dipeptide repeat protein (DPR) levels in CSF • To evaluate the biological activity of AL001 as measured by exploratory PD biomarkers of neurodegeneration, inflammation, lysosomal function, and glial activation in the blood, urine, and CSF • To evaluate the effect of AL001 on clinical measures of disease progression • To evaluate the effect of AL001 on ventilation-free survival • To estimate correlations between fluid PD biomarkers and clinical measures of disease progression
Endpoints	Primary Outcome Measures: • Safety: Defined as the occurrence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (SAEs), and treatment-emergent clinically significant abnormalities in clinical and laboratory values • Tolerability: Defined as the percentage of subjects who complete the study without TEAEs leading to treatment discontinuation • PK: Serum and CSF concentrations of AL001, and PK parameters • PD: Changes from baseline in plasma and CSF levels of PGRN • Immunogenicity: Incidence of ADAs to AL001
	Secondary Outcome Measures: • Changes in blood and CSF levels of NfL
	Exploratory Outcome Measures: • Pharmacogenetic effects of AL001 with respect to the following single nucleotide polymorphisms (SNPs): rs5848, [redacted] • Changes in CSF levels of poly (GP) DPRs • Changes in PD biomarkers of neurodegeneration, inflammation, lysosomal function, and glial activation in the blood, urine, and CSF

	• Clinical progression as measured by changes in: – ALS Functional Rating Scale-Revised (ALSFRS-R) total and domain scores – Combined Assessment of Function and Survival (CAFS) – Vital capacity (VC) – ALS Cognitive Behavioral Screen (ALS-CBS) – Digital home measures of cognition and motor speech components • Permanent assisted ventilation (PAV)-free survival • Correlations between fluid PD biomarkers and clinical measures of disease progression
Subject Selection	**Inclusion Criteria:** A prospective subject must meet all the following criteria to be eligible for study participation: 1. Diagnosis of *C9orf72*-associated ALS with both of the following: a. Documentation of a clinical genetic test demonstrating the presence of a pathogenic repeat expansion in *C9orf72* ***and*** b. Must meet possible, laboratory-supported probable, probable, or definite criteria for a diagnosis of ALS by revised El Escorial criteria (Brooks 2000). 2. Age 18 or older. 3. Capable of providing informed consent at the Screening Visit and complying with study procedures throughout the study, in the investigator's opinion and at the discretion of the Medical Monitor and the study sponsor. 4. If the subject has a participating caregiver, the caregiver must live with the subject and, in the investigator's opinion, have adequate knowledge of the subject's daily activities and function; participating caregivers must sign the caregiver section of the informed consent. Not having a caregiver is not exclusionary. 5. Time since onset of muscle weakness due to ALS ≤36 months at the time of the Screening Visit. 6. Vital capacity ≥50% of predicted capacity at the time of the Screening Visit. Vital capacity is preferred to be measured by slow vital capacity (SVC) in clinic. If required due to pandemic-related restrictions, forced vital capacity (FVC) measured in clinic via pulmonary function laboratory may be performed at the discretion of the Medical Monitor and the study sponsor. If due to

	pandemic-related restrictions in clinic vital capacity is not possible, then FVC may be performed via home spirometry at the discretion of the Medical Monitor and the study sponsor. 7. Must not be taking riluzole or must be on a stable dose of riluzole for at least 30 days prior to the Screening Visit. Riluzole-naïve patients are permitted in the study. 8. Must not be taking edaravone or must have completed at least one cycle of edaravone with a plan of continuing edaravone prior to the Screening Visit. Subjects must be off cycle and at least 2 days after the last dose administration of edaravone at the time of study drug infusions. Edaravone-naïve subjects are permitted in the study. 9. At Screening, women must be non-pregnant (as demonstrated by a negative serum pregnancy test at Screening) and non-lactating, and one of the following conditions must apply: a. Not a woman of childbearing potential (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 woman of childbearing potential and agrees to use an acceptable contraceptive method from Screening until 10 weeks after the last dose of study treatment. Acceptable contraception is defined as using hormonal contraceptives (eg, combined oral contraceptive pill) or an intrauterine device combined with at least one of the following forms of contraception: a diaphragm or cervical cap, or a condom. Total abstinence, if in accordance with the usual lifestyle of female subject, is acceptable. A woman of childbearing potential must have a serum pregnancy test conducted at Screening. Additional requirements for pregnancy testing during and after study intervention are described in the Schedule of Assessments (Appendix 1). 10. Men must agree to use acceptable contraception and not donate sperm from Day 0 until 10 weeks after the last dose of study treatment. Acceptable contraception for male subjects when having sexual intercourse with a female partner is defined as using a condom or having a vasectomy. In addition, female partners of childbearing potential must agree to use hormonal contraceptives (eg, combined oral contraceptive pill) or an intrauterine device. Total abstinence, if in accordance with the usual lifestyle of the male subject, is acceptable. 11. In the investigator's opinion, subjects must be able to complete all study procedures, including the IV study drug administration and lumbar punctures (LPs).

Exclusion Criteria:

Prospective subjects who meet any of the following criteria are not eligible for study participation:

1. Clinically significant, unstable, medical condition (other than ALS) that would pose a risk to the subject or interfere with the interpretation of study data, according to the investigator's judgement (eg, cardiovascular disease, systemic infection, pulmonary disease, rheumatologic disease, etc.).
2. Clinically significant laboratory abnormalities including, but not limited to: hemoglobin <10 g/dL, white blood cells (WBC) $<3.0 \times 10^3/mm^3$, absolute neutrophils $\leq 1.0 \times 10^3/mm^3$, eosinophilia (absolute eosinophil count of $\geq 0.5 \times 10^3/mm^3$), low platelet counts ($<150 \times 10^3/mm^3$), prothrombin time (PT)/activated partial thromboplastin time (aPTT)/international normalized ratio (INR), lipase ≥1.2 × upper limit of normal (ULN). Out-of-range laboratory abnormalities may be repeated during the Screening period to reassess for eligibility.
3. Subject has impaired hepatic function or occult liver injury as indicated by Screening:
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 3 times the ULN (bilirubin levels should be normal)
   b. Total bilirubin greater than 1.2 × ULN (with exception of Gilbert's syndrome)
   c. Alkaline phosphatase (ALP) equal to or higher than 2 × ULN unless the ALP elevation is not from a hepatic origin.

   Note: Out-of-range laboratory abnormalities may be repeated during the Screening period to reassess for eligibility.
4. Subject has significant kidney disease as indicated by either of the following:
   a. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2, according to Modification of Diet in Renal Disease (MDRD) Study equation. MDRD equation is as follows:

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

      or

   b. Creatinine ≥2 mg/dL.

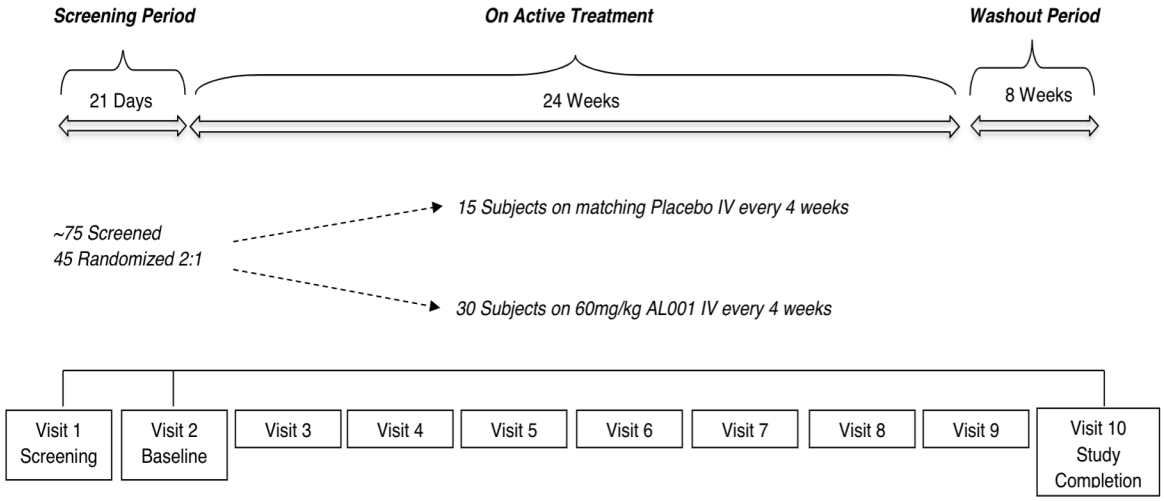
   Out-of-range laboratory abnormalities may be repeated during the Screening period to reassess for eligibility.

	5. Subject is positive for hepatitis B surface antigen (HbsAg), human immunodeficiency virus (HIV)-1 or -2 antibodies or antigen, or history of spirochetal infection of the central nervous system (CNS) (eg, syphilis, borreliosis, or Lyme disease). Subjects with a positive hepatitis C virus antibody will be allowed if hepatitis C RNA is negative. 6. Subject has uncontrolled hypertension (eg, repeated supine systolic blood pressure (BP) >140 mm Hg or diastolic BP >90 mm Hg) at Screening. 7. Subject has a history or presence of an abnormal electrocardiogram (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. 8. Presence of unstable psychiatric disease (including suicidality), cognitive impairment, dementia, or substance abuse that would impair ability of the subject to provide informed consent or interfere with the interpretation of study data, in the investigator's opinion. 9. Subject has a history of cancer, except if the subject: a. Is considered likely to be cancer-free b. Is not being actively treated with anticancer therapy or radiation and, in the opinion of the investigator, is not likely to require treatment in the ensuing 3 years. Ongoing antihormonal adjuvant treatment (eg, tamoxifen) is permitted c. Is considered to have low probability of recurrence (with supporting documentation from the treating oncologist and at the discretion of the investigator and Medical Monitor) d. For prostate cancer, has not had significant progression within the past 2 years. 10. Known history of severe allergic, anaphylactic, or other hypersensitivity reaction to chimeric, human, or humanized antibodies or proteins. 11. Any prior exposure to an anti-sortilin antibody. 12. Use of investigational treatments or nutritional supplements (off-label use or active participation in a clinical trial) within 5 half-lives (if known) or 30 days (whichever is longer) prior to the Screening Visit, at the discretion of the Medical Monitor and study sponsor. 13. Exposure at any time to any gene therapies under investigation for the treatment of ALS (off-label use or investigational)

	14. Unwilling to forgo donation of blood or blood products for transfusion for the duration of the study and for 1 year after final dose of study drug. 15. Anything that would place the subject at increased risk or preclude their full compliance with or completion of the study, in the investigator's opinion. 16. Contraindication to undergoing a LP, in the investigator's opinion. Subjects undergoing the LP must not be currently taking anticoagulation or antiplatelet medications, such as warfarin or Plavix®, that would be a contraindication to LP; aspirin and non-steroidal anti-inflammatories are allowed. 17. The following medications are prohibited for a pre-specified duration prior to study start, as indicated, and during the entire period of study participation (subjects who start these medications during the study may be discontinued from study drug administration): a. Any cannabinoids at least 90 days prior to study treatment administration unless approved by the Medical Monitor. Use of cannabinoids (other than cannabidiol [CBD]) is prohibited within 72 hours prior to any cognitive or behavioral assessment in the study. b. Any passive immunotherapy (immunoglobulin) or other long-acting biologic agent within 180 days of Screening c. Any experimental vaccine. Routinely recommended vaccinations are allowed, as well as any vaccine against SARS-CoV-2 (COVID-19) either approved or administered under an Emergency Use Authorization. d. Typical antipsychotic or neuroleptic medication within 180 days of study drug administration, except as brief treatment for a nonpsychiatric indication (eg, emesis). 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. Use of certain atypical antipsychotics may be allowed for as needed (PRN) or acute use at the discretion of the investigator, but must not be initiated within 48 hours of cognitive or behavioral assessments. e. Systemic immunosuppressive therapy, or the anticipated need for systemic immunosuppressive therapy during the study. 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 >10 g/dL, WBC count >$3.0 \times 10^3/mm^3$, absolute neutrophil count >$1.0 \times 10^3/mm^3$, and platelet count >150 $10^3/mm^3$. Brief use of systemic corticosteroids (≤7 days) is permitted for treatment of intercurrent illness.

	f. Chronic use of opiates or opioids (including long-acting opioid medication) within 90 days of study drug administration. 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 clinical outcome assessment. g. Chronic use of barbiturates, or hypnotics from 90 days prior to study drug administration. Intermittent short-term (<1 week) use of buspirone or a 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.
Study Duration	Enrollment is expected to take 8 to 10 months. Total Screening and Follow-up duration for each subject is 35 weeks. The time from first subject enrolled to last subject completed is expected to be 17 to 19 months.
Duration of Subject Participation	The expected total duration of a subject's participation is 35 weeks: Screening Period: 3 weeks Treatment Period: 24 weeks Follow-up Period: 8 weeks

Figure 1: Study Schema



Abbreviations: IV=intravenous.
Note: Subjects who plan to discontinue the study early should be encouraged to return to the investigational site for an Early Termination Visit, which is 8 weeks after the last dose of study treatment.

LIST OF TERMS AND ABBREVIATIONS

Abbreviation	Term
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event/adverse experience
ALP	alkaline phosphatase
ALS	amyotrophic lateral sclerosis
ALS-CBS	ALS Cognitive Behavioral Screen
ALT	alanine aminotransferase
aPTT	activated prothromboplastin time
AST	aspartate aminotransferase
BP	blood pressure
BMI	body mass index
ALSFRS-R	ALS Functional Rating Scale-Revised
AST	aspartate aminotransferase
C	Celsius
CAFS	Combined Assessment of Function and Survival
CC	Coordination Center
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
COVID-19	Coronavirus Disease 2019
C9ALS	*C9orf72*-associated amyotrophic lateral sclerosis
CBD	cannabidiol
cm	centimeter
CNS	central nervous system
CRA	clinical research associate
CRF	case report form
CRO	clinical research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
dL	deciliter
DLAE	dose-limiting adverse events

Abbreviation	Term
DNA	deoxyribonucleic acid
DPR	dipeptide repeat protein
eCRF	electronic Case Report Form
eGRF	estimated glomerular filtration rate
ECG	electrocardiogram
EDC	electronic data capture
EOS	end of study
F	Fahrenheit
FTD	frontotemporal dementia
FTD *C9orf72*	frontotemporal dementia with *C9orf72* hexanucleotide repeat expansion mutations
FTD-*GRN*	frontotemporal dementia with heterozygous progranulin gene mutations
FDA	Food and Drug Administration
FVC	forced vital capacity
g	grams
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GRN	progranulin gene
HbsAg	hepatitis B surface antigen
Hg	mercury
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iDMC	independent data monitoring committee
IEC	Independent Ethics Committee
IgG	immunoglobulin G
in	inches
IND	Investigational New Drug
INR	international normalized ratio

Abbreviation	Term
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	Interactive Response Technology
ISF	investigator site file
ITT	intent-to-treat
IV	intravenous
kg	kilogram
LFTs	liver function tests
LP	lumbar puncture
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MGH	Massachusetts General Hospital
MM	Medical Monitor
[redacted]	[redacted]
mm	millimeter
mM	millimolar
mmHg	millimeters of mercury
NCRI	Neurological Clinical Research Institute
NEALS	Northeast ALS Consortium
NfL	neurofilament light chain
OHRP	Office for Human Research Protections
PAV	permanent assisted ventilation
PD	pharmacodynamic
PGRN	progranulin
PI	Principal Investigator
PK	pharmacokinetic
PRN	*pro re nata*, meaning "as needed"
PT	partial thrombin
PTT	partial thromboplastin time
QA	quality assurance
QC	quality control

Abbreviation	Term
RAN	repeat associated non-AUG
RNA	ribonucleic acid
SAE	serious adverse event
SI	Site Investigator
SNP	single nucleotide polymorphism
SOP	standard operating procedure
SUSAR	serious, unexpected, suspected adverse drug reaction
SVC	slow vital capacity
TDP-43	TAR DNA-binding protein
TEAE	treatment-emergent adverse event
TMF	Trial Master File
ULN	upper limit of normal
US	United States
VC	vital capacity
WHO	World Health Organization

1. INTRODUCTION

1.1. Study Rationale

1.1.1. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive disorder affecting the motor neurons in the brain and spinal cord, ultimately leading to paralysis and death from respiratory failure (Brooks 1996). The incidence of ALS is approximately 2/100,000, with a prevalence of only 5/100,000 due to rapid disease progression (Chiò 2013). Median age of onset is in the mid-to-late 50s, with survival variable and often dependent on phenotype (Brown 2017). Riluzole and edaravone, the two Food and Drug Administration (FDA)-approved disease-modifying medications for ALS, confer only a modest survival benefit (Miller 2012; Writing Group; Edaravone (MCI-186) ALS 19 Study Group 2017).

1.1.2. *C9orf72*-Associated ALS

An expansion of the hexanucleotide intronic repeat GGGGCC in the *C9orf72* (C9) gene was first described in 2011 and is the most common cause of familial ALS (DeJesus-Hernandez 2011; Renton 2011; Gijselinck 2012). Approximately 40-50% of all familial ALS and up to 10% of sporadic ALS cases are attributed to this repeat expansion. Patients harboring the C9 repeat expansion have an increased predilection for bulbar-onset and the coincidence of frontotemporal dysfunction (Ghasemi 2018). The proposed mechanisms by which the C9 repeat expansion causes disease are RNA and protein-mediated neurotoxicity through accumulation of dipeptide repeat proteins (DPRs) from repeat associated non-AUG (RAN) translation and RNA binding protein (eg, TDP-43) sequestration (Brown 2017). TAR DNA-binding protein 43 (TDP-43) is an RNA/DNA binding protein important to RNA-related metabolism, found within deposits or inclusion bodies in the brains and spinal cords of patients with both sporadic and familial forms of ALS and frontotemporal dementia (FTD), including individuals with *C9orf72*-associated ALS (C9ALS) (Prasad 2019; Steinacker 2016).

1.1.3. Shared Genetics and Pathology of ALS and Frontotemporal Dementia

There is increasing evidence of not only a clinical co-occurrence but a genetic overlap between ALS and FTD (Karch 2018). Multiple genes have been identified as causative for both disorders, including TARDBP, *C9orf72*, VCP, and TBK1 (Weishaupt 2016; Smith 2012). The locus of the FTD causal gene, progranulin gene (*GRN*), carries a functional single nucleotide polymorphism (SNP) (rs5848) that is linked to survival after disease onset in C9 repeat expansion carriers (van Blitterswijk 2014). Furthermore, common variants in *GRN* ([redacted]) were significantly associated with an earlier age of onset and a sho e survival in individuals with ALS (Sleegers 2008). These data not only indicate that progranulin (PGRN) genetic variability acts as a modifier in ALS, but a common pathway by which *C9orf72* and PGRN cause disease.

TDP-43 is an RNA/DNA binding protein important to RNA-related metabolism, found within deposits or inclusion bodies in the brain and spinal cord of patients with both sporadic and familial forms of ALS and FTD, including individuals with C9ALS (Prasad 2019; Steinacker 2016). The prevalence of TDP-43 in most forms of ALS and tau-negative FTD

(Van Mossevelde 2018) suggests a pivotal pathogenic role, and thus pathways impacting TDP-43 aggregation are potential therapeutic targets in these fatal diseases (Scotter 2015; Shenouda 2018).

Chronic inflammation is another common pathogenic feature seen in ALS and FTD, suggesting the importance of central nervous system (CNS) immune cells such as microglia in both diseases. *GRN* and *C9orf72* mutations are also both associated with abnormal microglial activation (Haukedal 2019). PGRN is a highly expressed protein in microglial cells, with multiple functions including modulation of inflammation (Haukedal 2019), regulation of lysosomal function (Tanaka 2013), and neurotrophic effects including preservation of neuronal survival and axonal growth (Gass 2012, De Muynck 2013). PGRN deficiency results in an exaggerated inflammatory response after brain insults (Tanaka 2013; Martens 2012; Yin 2010).

PGRN was shown to reverse and be protective against TDP-43 pathology in preclinical studies (Laird 2010; Tauffenberger 2013, Chang 2017; Beel 2018), which characterizes approximately 95% of all ALS cases (Prasad 2019). While loss of PGRN was found to be detrimental in multiple models of acute and chronic neurodegeneration (Boddaert 2018), overexpression of PGRN was protective. Specifically, overexpression of human PGRN was protective against TDP-43-induced axonopathy in a zebrafish model (Laird 2010). PGRN was also shown to be protective in a *C. elegans* model of TDP-43 and FUS-induced polyglutamine toxicity (Tauffenberger 2013). PGRN overexpression in TDP-43(A315T) mice reduced the levels of insoluble TDP-43, decreased the loss of large motor axon fibers, and prolonged survival by approximately 130 days (Beel 2018). These findings are consistent with Chang et. al, suggesting impaired autophagy contributes to the accumulation of TDP-43 in $GRN^{-/-}$ neurons, and that PGRN can stimulate clearance of TDP-43 through autophagy (Chang 2017). In contrast, overexpression of PGRN in mutant SOD1 mice, a model of a human ALS form that is not associated with TDP-43 pathology, did not affect onset or progression of motor neuron degeneration (Herdewyn 2013), indicating that the effect of PGRN is specific to TDP-43 pathology.

1.2. Background

1.2.1. Sortilin and AL001

Human and mouse genetic studies identified the transmembrane receptor sortilin, encoded by the *SORT1* gene, as the major negative regulator of PGRN levels in plasma and the brain (Carrasquillo 2010; Hu 2010). Sortilin binds PGRN and targets it for lysosomal degradation resulting in a reduction of extracellular PGRN.

AL001 is an intravenous (IV) recombinant monoclonal antibody (known as latozinemab but referred to as AL001 within the protocol) that selectively binds to human and cynomolgus monkey sortilin. Sortilin induces the degradation of PGRN (Carrasquillo 2010; Hu 2010), and its blockade leads to a chronic, 2–3-fold increase in plasma and cerebrospinal fluid (CSF) levels of PGRN in cynomolgus monkeys and in healthy human volunteers. Blocking sortilin/PGRN interactions, therefore, provides a therapeutic strategy for sustaining PGRN levels in the CNS.

Sortilin is not required for PGRN signaling, as evidenced by the fact that *SORT1*-deficient neurons retain a full response to PGRN (Gass 2012), and interestingly, *SORT1* knockout is not associated with neurodegeneration (Jansen 2007).

1.2.2. Overview of Nonclinical Toxicology Studies

To support clinical studies, the toxicology of AL001 was evaluated via single- and repeat-dose preliminary and Good Laboratory Practice (GLP) repeat-dose (4-week and 26-week) IV toxicology studies in cynomolgus monkeys. Across all the dose levels assessed (up to [redacted] mg/kg), there were no significant toxicology findings in the nonclinical studies.

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

1.2.3. Overview of Clinical Studies with AL001

AL001 is currently in evaluation for the treatment of FTD with TDP-43 pathology and in C9ALS.

Study AL001-1, Phase 1 FIH Study in Healthy Volunteers and Patients with FTD (Completed): The AL001 dose was determined based on the results from a Phase 1 dose-finding study in healthy volunteers and in patients with FTD (Study AL001-1). A total of 52 healthy volunteers received single doses of AL001 ranging from 2 mg/kg to 60 mg/kg and 12 subjects received placebo. AL001 was generally safe and well tolerated through the highest dose assessed (60 mg/kg) and demonstrated a favorable safety profile without dose-limiting toxicities or concerning apparent trends in adverse events (AEs), with a robust pharmacodynamics (PD) effect in plasma and CSF. The second part of Study AL001-1 enrolled asymptomatic FTD-*GRN* patients who received a single dose of 60 mg/kg AL001 by IV, and symptomatic FTD-*GRN* patients who received 3 doses of IV 30 mg/kg AL001 every 2 weeks. Data showed safety and tolerability, while demonstrating proof-of-mechanism of action with prolonged post-dose increase in plasma PGRN concentration.

Study AL001-2, A Phase 2 Open-Label Extension Study in Patients with FTD (Ongoing): Study AL001-2 is evaluating the long-term safety profile of AL001 in symptomatic and asymptomatic FTD-*GRN* carriers, and in symptomatic carriers of *C9orf72* mutations causative of FTD (FTD *C9orf72*). As of 27 August 2021, a total of 16 *GRN* carriers (5 asymptomatic and 11 symptomatic with FTD) and 9 symptomatic *C9orf72* carriers with FTD have been enrolled; study AL001-2 will enroll up to 20 symptomatic FTD *C9orf72* repeat expansion carriers. The most frequently reported treatment-emergent adverse events (TEAEs) across all study populations have been fall and rash.

Study AL001-3, A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study in Patients with FTD: Study AL001-3 is evaluating the efficacy and safety of AL001 in individuals with symptomatic FTD and at-risk *GRN* mutation carriers. The study is ongoing and remains blinded. As of the 27 August 2021 data cutoff, 38 subjects have been enrolled. There have been no deaths, no drug-related SAEs, and AEs have been predominantly mild in severity. One moderate TEAE of flagellate dermatitis led to study discontinuation.

Refer to the AL001 Investigator's Brochure for additional clinical study data.

1.2.4. Rationale for the Treatment of C9ALS with AL001

The accumulation of TDP-43 is the most significant pathological finding in approximately 95% of ALS cases, such as those associated with the C9 repeat expansion (Prasad 2019). Both data from animal models and human genetics support a neuroprotective effect of increasing

extracellular PGRN levels by reducing TDP-43-associated pathology in ALS. Taken together, these findings suggest that AL001 may be a candidate therapeutic in C9ALS.

1.2.5. Dose Justification

The AL001 dose was determined based on the AL001-1 Phase 1 study results. AL001 was generally safe and well tolerated through the highest dose assessed (60 mg/kg) and demonstrated a favorable safety profile without dose-limiting adverse events (DLAEs), with a robust PD effect in plasma and CSF.

1.3. Risk/Benefit Assessment of AL001

Refer to the AL001 Investigator's Brochure 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 and AL001-ALS-201 Study Procedures and Assessments

Risks Associated with AL001-ALS-201 Study Procedures and Assessments: The study procedures and assessments to be performed are not considered to be of great burden to subjects and are not associated with high risk.

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

Serious Adverse Drug Reactions: No serious adverse drug reactions (ADRs) have been reported in completed and ongoing clinical studies with AL001 to date 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 subjects receiving single-dose AL001 or three doses of AL001 administered every 2 weeks. Based on the current information from studies with AL001, the impact of immunogenicity on AL001 exposure, PD effects, and clinical safety do not appear consequential with short duration of exposure. However, the impact of ADAs continues to be assessed in ongoing AL001 clinical studies with longer-term exposure. An ADA assay for neutralizing antibodies to AL001 is under development. See the AL001 Investigator's Brochure for more information on immunogenicity.

Adverse Events: AL001 has been generally safe and well tolerated. There have been no deaths, no AL001-related serious adverse events (SAEs), and no AL001-related 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 AL001 Investigator's Brochure for a detailed summary of AEs.

1.3.3. Potential Benefits of AL001

AL001 is a novel recombinant human monoclonal immunoglobulin G (IgG)1 antibody that blocks sortilin, decreasing the rate of PGRN clearance, and raising the concentration of PGRN. AL001 may therefore decrease the rate of neurodegeneration associated with ALS among

patients who carry *GRN* mutations. Treatment with AL001 represents a promising therapeutic strategy for patients with C9ALS and while the efficacy of treatment with AL001 is still under investigation, patients with C9ALS may benefit from participating in clinical trials of AL001, which are designed to evaluate a potential treatment for a disease for which there are inadequate treatments. Subjects will receive either AL001 or placebo in addition to their stable, standard of care treatment. All subjects 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 Assessment for Study AL001-ALS-201 Study Subjects

Participation in Study AL001-ALS-201 offers the possibility of receiving AL001, a novel recombinant human monoclonal IgG1 antibody that blocks sortilin, for the treatment of adults with C9ALS. 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 ALS among patients who carry *C9orf72* mutations.

More detailed information about the known and expected benefits and risks of AL001 may be found in the AL001 Investigator's Brochure.

The potential benefit of AL001 to subjects is based on the completed Phase 1 study, 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 and increased plasma PGRN 2-3× in FTD subjects with *C9orf72* mutations. By blocking sortilin, decreasing the rate of PGRN clearance and therefore raising the extracellular concentration, AL001 may reduce TDP-43-associated pathology and decrease the rate of neurodegeneration and clinical decline associated with ALS among patients who carry *C9orf72* mutations (C9ALS).

Any risks to subjects in AL001-ALS-201 will be minimized through a combination of screening for appropriate eligibility criteria and rigorous safety monitoring to identify risks, as well as careful toxicity management. Adverse event and/or severe AE 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 risk/benefit profile of AL001 are appropriately reported and managed. Alector will provide careful screening, diligent monitoring, and management of patient safety throughout the course of the study.

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 in this study. 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. Periodic 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 assessed. An independent data monitoring committee (iDMC) with the capability of reviewing unblinded data will provide additional oversight of the study, supplementing the Sponsor’s screening, monitoring, and management of patient safety. 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 subjects who may not have legal capacity to provide consent. Therefore, it is plausible to conclude that the anticipated benefits of participating in this study outweigh the potential risks or inconveniences.

2. OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
• To evaluate the safety of AL001 in C9ALS • To evaluate the tolerability of AL001 in C9ALS • To evaluate changes in plasma and CSF PGRN levels after AL001 treatment • To evaluate AL001 PK parameters in serum and CSF • To evaluate ADAs to AL001 in serum	• Safety: Defined as the occurrence of TEAEs, treatment-emergent SAEs, and treatment-emergent clinically significant abnormalities in clinical and laboratory values • Tolerability: Defined as the percentage of subjects who complete the trial without TEAEs leading to treatment discontinuation • PK: Serum and CSF concentrations of AL001, and PK parameters • PD: Changes from baseline in plasma and CSF levels of PGRN • Immunogenicity: Incidence of ADAs to AL001	Safety, tolerability, immunogenicity, PK, CSF penetration of AL001, and PD have not yet been evaluated in patients with C9ALS.
Secondary		
• To evaluate the biological activity of AL001 as measured by NfL levels in the blood and CSF	• Changes in blood and CSF levels of NfL	The level of neurofilament, a marker of neurodegeneration, is believed to be relatively stable over time and thus, a change from baseline may demonstrate biological evidence of a disease modifying effect.
Exploratory		
• To evaluate genotype-specific effects of AL001 on PD biomarkers for common variants of *GRN* • To evaluate dipeptide repeat protein (DPR) levels in CSF • To evaluate the biological activity of AL001 as measured by exploratory PD biomarkers of neurodegeneration, lysosomal	• Pharmacogenetic effects of AL001 with respect to the following single nucleotide polymorphisms (SNPs): rs5848, [redacted] • Changes in CSF levels of poly (GP) DPRs • Changes in PD biomarkers of neurodegeneration, lysosomal	These endpoints have been chosen to provide a greater understanding of ALS and may provide opportunities for identification of surrogate endpoints that are reasonably likely to predict clinical benefit and that might serve as a basis for accelerated approval in future trials.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
function, and glial activation in the blood, urine, and CSF • To evaluate the effect of AL001 on clinical measures of disease progression • To evaluate the effect of AL001 on ventilator-free survival • To estimate correlations between fluid PD biomarkers and clinical measures of disease progression	function, and glial activation in the blood, urine, and CSF • Clinical progression as measured by changes in: – ALS Functional Rating Scale-Revised (ALSFRS-R) total and domain scores – Combined Assessment of Function and Survival (CAFS) – Vital capacity (VC) – ALS Cognitive Behavioral Screen (ALS-CBS) – Digital home measures of cognition and motor speech components • Permanent assisted ventilation (PAV)-free survival • Correlations between fluid PD biomarkers and clinical measures of disease progression	

Abbreviations: ADA=anti-drug antibody; AE=adverse event; ALS=amyotrophic lateral sclerosis; ALS-CBS=ALS Cognitive Behavioral Screen; ALSFRS-R=ALS Functional Rating Scale-Revised; CSF=cerebrospinal fluid; DPR=dipeptide repeat protein; IV= intravenous; NfL=neurofilament light chain; PAV=permanent assisted ventilation; PGRN=progranulin; PD=pharmacodynamic; PK=pharmacokinetic; SAE=serious adverse event; SNP=single nucleotide polymorphism; TEAE=treatment-emergent adverse event; VC=vital capacity.

3. STUDY DESIGN

3.1. Overall Design

This is a Phase 2, multicenter, randomized clinical trial evaluating the safety, tolerability, and biological effect of AL001 compared to placebo in approximately 45 adults with C9ALS.

The study consists of a Screening Period (within 3 weeks prior to Day 0), a 24-week Treatment Period, and an 8-week Safety Follow-Up Period, concluding with the Study Completion Visit (8 weeks after last study drug administration).

Informed consent will be obtained prior to the conduct of any study-related procedures. Any individual who gives written informed consent to participate in the study is considered a subject in the study. Subject eligibility will be assessed at the Screening Visit and during the Screening Period. Upon determination of subject eligibility, Day 0 will occur within 3 weeks of Screening.

Subjects will be randomly assigned to receive either standard of care + AL001 or standard of care + placebo (randomized 2:1 with stratification by rs5848 genotype [CC, CT, TT]). AL001 60 mg/kg or matching placebo will be administered via IV infusion every 4 weeks for 24 weeks.

An iDMC will review the progress of the study and perform safety reviews to evaluate potential safety and tolerability issues. The iDMC will be governed by an approved charter. The roles and responsibilities of the iDMC are summarized in Section 10.5.

Refer to the Schedule of Assessments (Appendix 1) for the assessments to be performed at each study visit.

3.2. End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Assessments (Appendix 1).

Subjects can withdraw from the study at any time. Subjects who plan to discontinue the study early should be encouraged to return to the investigational site for an Early Termination Visit, which is 8 weeks after the last dose of study treatment.

Information on whether a subject has died may be obtained from the subject's family, from clinic notes, or from a publicly available data source like the Centers for Disease Control and Prevention (CDC) National Death Index or the Social Security Death Index. The vital status determination, defined as a determination of date of death or death equivalent or date last known alive, can be determined for each subject at the end of their study participation. If the subject is alive at the end of their study participation, their vital status may be determined again at a later time after study participation has ended but before the final data lock from clinic notes or using publicly available resources.

4. STUDY POPULATION

4.1. Inclusion Criteria

A prospective subject must meet all the following criteria to be eligible for study participation:

1. Diagnosis of *C9orf72*-associated ALS with both of the following:
   a. Documentation of a clinical genetic test demonstrating the presence of a pathogenic repeat expansion in *C9orf72*

      and

   b. Must meet possible, laboratory-supported probable, probable, or definite criteria for a diagnosis of ALS by revised El Escorial criteria (Brooks 2000).
2. Age 18 or older.
3. Capable of providing informed consent at the Screening Visit and complying with study procedures throughout the study, in the investigator's opinion and at the discretion of the Medical Monitor and the study sponsor.
4. If the subject has a participating caregiver, the caregiver must live with the subject and, in the investigator's opinion, have adequate knowledge of the subject's daily activities and function; participating caregivers must sign the caregiver section of the informed consent. Not having a caregiver is not exclusionary.
5. Time since onset of muscle weakness due to ALS ≤36 months at the time of the Screening Visit.
6. Vital capacity (VC) ≥50% of predicted capacity at the time of the Screening Visit. Vital capacity is preferred to be measured by slow vital capacity (SVC) in clinic. If required due to pandemic-related restrictions, forced vital capacity (FVC) measured in clinic via pulmonary function laboratory may be performed at the discretion of the Medical Monitor and the study sponsor. If due to pandemic-related restrictions in clinic vital capacity is not possible, then FVC may be performed via home spirometry at the discretion of the Medical Monitor and the study sponsor.
7. Must not be taking riluzole or must be on a stable dose of riluzole for at least 30 days prior to the Screening Visit. Riluzole-naïve patients are permitted in the study.
8. Must not be taking edaravone or must have completed at least one cycle of edaravone with a plan of continuing edaravone prior to the Screening Visit. Subjects must be off cycle and at least 2 days after the last dose administration of edaravone at the time of study drug infusions. Edaravone-naïve subjects are permitted in the study.
9. At Screening, women must be non-pregnant (as demonstrated by a negative serum pregnancy test at Screening) and non-lactating, and one of the following conditions must apply:
   a. Not a woman of childbearing potential (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 woman of childbearing potential and agrees to use an acceptable contraceptive method from Screening until 10 weeks after the last dose of study treatment. Acceptable contraception is defined as using hormonal contraceptives (eg, combined oral contraceptive pill) or an intrauterine device combined with at least one of the following forms of contraception: a diaphragm or cervical cap, or a condom. Total abstinence, if in accordance with the usual lifestyle of female subject, is acceptable.

A woman of childbearing potential must have a serum pregnancy test conducted at Screening. Additional requirements for pregnancy testing during and after study intervention are described in the Schedule of Assessments (Appendix 1).

10. Men must agree to use acceptable contraception and not donate sperm from Day 0 until 10 weeks after the last dose of study treatment. Acceptable contraception for male subjects when having sexual intercourse with a female partner who is not currently pregnant is defined as using a condom. In addition, female partners of childbearing potential must agree to use hormonal contraceptives (eg, combined oral contraceptive pill) or an intrauterine device. Acceptable contraception for male subjects when having sexual intercourse with a female partner is defined as using a condom or having a vasectomy. Total abstinence, if in accordance with the usual lifestyle of the male subject, is acceptable.
11. In the investigator's opinion, subjects must be able to complete all study procedures, including the IV study drug administration and lumbar punctures (LPs).

4.2. Exclusion Criteria

Prospective subjects who meet any of the following criteria are not eligible for study participation:

1. Clinically significant, unstable, medical condition (other than ALS) that would pose a risk to the subject or interfere with the interpretation of study data, according to the investigator's judgement (eg, cardiovascular disease, systemic infection, pulmonary disease, rheumatologic disease, etc.).
2. Clinically significant laboratory abnormalities including, but not limited to: hemoglobin <10 g/dL, white blood cells (WBC) $<3.0 \times 10^3/mm^3$, absolute neutrophils $\leq 1.0 \times 10^3/mm^3$, eosinophilia (absolute eosinophil count of $\geq 0.5 \times 10^3/mm^3$), low platelet counts ($<150 \times 10^3/mm^3$), prothrombin time (PT)/activated partial thromboplastin time (aPTT)/international normalized ratio (INR), lipase >1.2 × upper limit of normal (ULN). Out-of-range laboratory abnormalities may be repeated during the Screening period to reassess for eligibility.
3. Subject has impaired hepatic function or occult liver injury as indicated by Screening:
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 3 times the ULN (bilirubin levels should be normal)
   b. Total bilirubin greater than 1.2 × ULN (with exception of Gilbert's syndrome)
   c. Alkaline phosphatase (ALP) equal to or higher than 2 × ULN unless the ALP elevation is not from a hepatic origin.

Note: Out-of-range laboratory abnormalities may be repeated during the Screening period to reassess for eligibility.

4. Subject has significant kidney disease as indicated by either of the following:
   a. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2, according to Modification of Diet in Renal Disease (MDRD) Study equation. MDRD equation is as follows:

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

      or

   b. Creatinine ≥2 mg/dL.

   Out-of-range laboratory abnormalities may be repeated during the Screening period to reassess for eligibility.
5. Subject is positive for hepatitis B surface antigen (HbsAg), human immunodeficiency virus (HIV)-1 or -2 antibodies or antigen, or history of spirochetal infection of the CNS (eg, syphilis, borreliosis, or Lyme disease). Subjects with a positive hepatitis C virus antibody will be allowed if hepatitis C RNA is negative.
6. Subject has uncontrolled hypertension (eg, repeated supine systolic blood pressure (BP) >140 mm Hg or diastolic BP >90 mm Hg) at Screening.
7. Subject has a history or presence of an abnormal electrocardiogram (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.
8. Presence of unstable psychiatric disease (including suicidality), cognitive impairment, dementia, or substance abuse that would impair ability of the subject to provide informed consent or interfere with the interpretation of study data, in the investigator's opinion.
9. Subject has a history of cancer, except if the subject:
   a. Is considered likely to be cancer-free
   b. Is not being actively treated with anticancer therapy or radiation and, in the opinion of the investigator, is not likely to require treatment in the ensuing 3 years. Ongoing antihormonal adjuvant treatment (eg, tamoxifen) is permitted.
   c. Is considered to have low probability of recurrence (with supporting documentation from the treating oncologist and at the discretion of the investigator and Medical Monitor).
   d. For prostate cancer, has not had significant progression within the past 2 years.
10. Known history of severe allergic, anaphylactic, or other hypersensitivity reaction to chimeric, human, or humanized antibodies or proteins.
11. Any prior exposure to an anti-sortilin antibody.
12. Use of investigational treatments or nutritional supplements (off-label use or active participation in a clinical trial) within 5 half-lives (if known) or 30 days (whichever is

longer) prior to the Screening Visit, at the discretion of the Medical Monitor and study sponsor.

13. Exposure at any time to any gene therapies under investigation for the treatment of ALS (off-label use or investigational).
14. Unwilling to forgo donation of blood or blood products for transfusion for the duration of the study and for 1 year after final dose of study drug.
15. Anything that would place the subject at increased risk or preclude their full compliance with or completion of the study, in the investigator's opinion.
16. Contraindication to undergoing a LP, in the investigator's opinion. Subjects undergoing the LP must not be currently taking anticoagulation or antiplatelet medications, such as warfarin or Plavix®, that would be a contraindication to LP; aspirin and non-steroidal anti-inflammatories are allowed.
17. The following medications are prohibited for a pre-specified duration prior to study start, as indicated, and during the entire period of study participation (subjects who start these medications during the study may be discontinued from study drug administration):
    a. Any cannabinoids at least 90 days prior to study treatment administration unless approved by the Medical Monitor. Use of cannabinoids (other than cannabidiol [CBD]) is prohibited within 72 hours prior to any cognitive or behavioral assessment in the study.
    b. Any passive immunotherapy (immunoglobulin) or other long-acting biologic agent within 180 days of Screening.
    c. Any experimental vaccine. Routinely recommended vaccinations are allowed, as well as any vaccine against SARS-CoV-2 (COVID-19) either approved or administered under an Emergency Use Authorization.
    d. Typical antipsychotic or neuroleptic medication within 180 days of study drug administration, except as brief treatment for a nonpsychiatric indication (eg, emesis). 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. Use of certain atypical antipsychotics may be allowed for as needed (PRN) or acute use at the discretion of the investigator, but must not be initiated within 48 hours of cognitive or behavioral assessments.
    e. Systemic immunosuppressive therapy, or the anticipated need for systemic immunosuppressive therapy during the study. 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 >10 g/dL, WBC count >3.0 × 10^3/mm^3, absolute neutrophil count >1.0 × 10^3/mm^3, and platelet count >150 10^3/mm^3. Brief use of systemic corticosteroids (≤7 days) is permitted for treatment of intercurrent illness.
    f. Chronic use of opiates or opioids (including long-acting opioid medication) within 90 days of study drug administration. 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 clinical outcome assessment.

g. Chronic use of barbiturates, or hypnotics from 90 days prior to study drug administration. Intermittent short-term (<1 week) use of buspirone or a 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.

4.3. Screening Failures

Individuals who give informed consent to participate in the clinical trial, but who do not meet one or more criteria required for participation in the trial during the screening assessments, are considered screening failures. Minimal information for subjects who fail screening is collected in the Interactive Response Technology (IRT) system; this information includes basic demography and the reason(s) the subject failed Screening.

Subjects who fail screening may be allowed one rescreen if an identifiable cause for screen failure is appropriately managed following approval of Alector's Medical Monitor. Subjects who are to be rescreened must be reconsented and given a new screening number, and the screening assessments must be repeated. The subject may not be required to repeat LP, if performed within 12 weeks prior to study treatment administration, with approval from Alector's Medical Monitor. Repeat pharmacogenomic sampling is not required.

5. IDENTITY OF INVESTIGATIONAL PRODUCT

5.1. AL001

AL001 is a human recombinant anti-human sortilin monoclonal IgG1 G1m17,1 [or G1m (z,a)] kappa monoclonal antibody).

5.2. Dosing and Administration

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

AL001 or placebo will be administered IV over 60 minutes (±15 minutes) by trained site personnel under the supervision of the investigator or their designee. Study treatment administration will be recorded in the source documentation and in the electronic Case Report Form (eCRF).

The investigator or a qualified designee must be present during the administration of study treatment. Subjects should be monitored for at least 60 minutes post infusion for the first 2 infusions of AL001. After the first 2 infusions, post-infusion monitoring may be reduced to 30 minutes. On treatment days, subjects will be discharged after the post-infusion monitoring period and after completion of all activities scheduled for that visit day at the discretion of the investigator or qualified designee.

5.3. Storage, Handling, and Stability

5.3.1. Storage and Handling

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

Upon receipt at the investigational site, the AL001 and placebo shall be stored securely under controlled conditions in a refrigerator set to maintain 2°C to 8°C. The AL001 and placebo vials should be protected from light and remain in the cartons provided until use. Specific instructions about the preparation and administration of investigational drug are provided in the Pharmacy Manual.

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

5.3.2. Stability of Prepared AL001 Solution

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.

5.4. Formulation, Packaging, and Labeling

5.4.1. Formulation

AL001 is provided as a sterile solution formulated at a concentration of [redacted] mg AL001/mL in an aqueous formulation containing [redacted].

The placebo shares the same formulation as the study drug but lacks the AL001 antibody.

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

5.4.2. Packaging and Labeling

The container closure system for both AL001 and placebo consists of a 20R Type I (European Pharmacopoeia compliant) clear glass vial with a coated bromobutyl rubber stopper and a flip-off type aluminum crimp seal with blue cap. Each single use vial will contain at least [redacted] mL of AL001 or [redacted] mL of placebo intended for IV use only.

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

5.5. Drug Accountability

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

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

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

5.6. Randomization and Blinding

5.6.1. Randomization

Eligible subjects will be randomized to AL001 or placebo in a 2:1 ratio with stratification by rs5848 genotype (3 levels: CC, CT, TT). Randomization schedules for each stratum will be computer generated using permuted blocks.

Subjects who sign the informed consent form and are randomized, but who do not receive study drug, may be replaced. Subjects who sign the informed consent form, are randomized, receive study drug, and who subsequently withdraw or are withdrawn from the study, will not be replaced.

Eligible subjects will be randomly assigned to AL001 or placebo based on a randomization schedule prepared by the clinical research organization (CRO) before the start of the study. An IRT system will be used to administer the randomization schedule.

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

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

5.6.2. Blinding

Blind maintenance procedures for the study are detailed in the Blind Maintenance Plan.

5.6.2.1. Blinded and Unblinded Personnel

Research subjects, investigators, and anyone involved in the conduct of, final analysis of, or with any other interest in the trial, with the exception of the iDMC and the independent statistical group supporting the iDMC, will be blinded to randomized treatment assignments. The randomized treatment assigned for subjects will be kept secure until final database lock.

In addition to the iDMC and the independent statistical group supporting the iDMC, safety personnel, and the administrative pharmacy personnel will be unblinded as needed.

The Sponsor may be unblinded to a participant's treatment assignment, if necessary, for safety (see Section 5.6.2.2).

5.6.2.2. Circumstances for Breaking the Blind

In the event of a medical emergency, an investigator may be unblinded to the treatment assignment of a single subject in order to safely provide care to that participant. Emergency unblinding for a subject will only be undertaken when knowing the participant's treatment assignment is essential to treating the subject safely or otherwise ensure the safety of other participants or others exposed to investigational products. The investigator may unblind an individual participant's treatment allocation through the IRT. Reasons for treatment unblinding must be clearly explained and justified in the source documents. The date on which the code was broken, together with the identity of the person responsible, must also be documented. Alector recommends but does not require that the investigator contact the Medical Monitor before breaking the blind. Treatment assignment should not be disclosed to the Medical Monitor.

Maintaining blinded treatment is critical for the integrity of the clinical study, and therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will be discontinued from study treatment, but will continue with study follow-up assessments and procedures, if possible.

Alector pharmacovigilance personnel may independently unblind a subject for expedited reporting of suspected unexpected serious adverse reactions (SUSARs) or other events requiring expedited regulatory reporting. In addition, in the event of SUSARs, which are subject to expedited reporting, Alector pharmacovigilance staff or their designee will unblind the affected cases in order to fulfill reporting requirements. For such cases, unblinding will be performed according to documented procedures and the unblinded information will be kept to authorized pharmacovigilance personnel.

5.7. Concomitant Therapy

Throughout the study, subjects may be prescribed concomitant medications deemed necessary by their treating clinician to provide adequate care. Subjects should not receive other investigational products during the study. This includes marketed agents at experimental dosages that are being

tested for the treatment of ALS. Subjects who have not started riluzole or edavarone prior to the study will not be allowed to initiate these medications during study treatment given their potential to interfere with study endpoint assessments. All concomitant medications and significant non-drug therapies, including supplements, received by a subject should be recorded from the point of screening forward on the appropriate source document and eCRF. Medications that are prohibited for a pre-specified duration prior to study start, and during the entire period of study participation are listed in Section 4.2, Item 17.

5.8. Infusion-Related Reactions

5.8.1. Guidance for Management of Infusion-Related Reactions

All subjects will be monitored for infusion-related reactions (IRR) or injection-related reactions during the infusion and immediately afterwards for at least 60 minutes post infusion for the first 2 infusions, and at least 30 minutes for subsequent infusions. Injection-related reactions can be localized at the site of the injection or systemic and should be treated per institutional guidelines. Acute IRRs typically occur within 24 hours of infusion and may manifest as erythema, pruritis, fever, or chills and progress to an anaphylactic-type reaction. Clinical sites should be prepared to manage any acute hypersensitivity or hypersensitivity-like events. Table 1 provides guidelines on management of acute infusion reactions as well as management of subsequent AL001 dosing.

In addition, in the event of an IRR, blood samples should be obtained for serum PK and ADA assessments of AL001 or placebo, and blood samples should be drawn for assessment by the laboratory: C-reactive protein (CRP), ferritin, tryptase, and IL-6 (at 1 to 2 hours after the IRR, then again at 48-72 hours after the IRR). Where possible, clinical laboratory samples should be drawn at the site for central laboratory; however, local laboratories may be utilized, and results assessed for safety by the investigator.

Further details regarding IRRs are provided in the Investigator Brochure.

Table 1: Guidelines for Management of Acute Infusion-Related Reactions

WHO Toxicity Criteria	Treatment	Pre-Medication at Subsequent Dosing
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	Stop infusion and monitor symptoms. If symptoms resolve without intervention, the infusion may be restarted at 50% of the original infusion rate.	None
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to IV fluids, antihistamines, and antipyretics. Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve following supportive treatment, the infusion may be restarted at 50% of the original infusion rate. Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate pre-medication and infusion rate reduction should be permanently discontinued from further trial treatment administration.	Subject should be premedicated prior to next dose of study drug with antihistamine (eg, diphenhydramine 50 mg po) and antipyretic (eg, acetaminophen / paracetamol 500-1000 mg po).
Grades 3 or 4 Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequalae Grade 4: Life-threatening consequences; urgent intervention indicated	Stop infusion and increase monitoring of vital signs as medically indicated. Additional appropriate medical therapy may include but is not limited to IV fluids, IV steroids (eg, hydrocortisone 100-200 mg or corticosteroid equivalent), IV antihistamines, vasopressors, and antipyretics. Hospitalization may be indicated. Subjects with signs or symptoms that may be consistent with cardiac etiology should be assessed by ECGs, cardiac enzymes (eg, creatinine-MB isoenzyme, troponins, brain natriuretic peptide) to rule out myocardial infarction, and echocardiogram should be performed unless cardiac failure is ruled out by preceding investigations. Subject is permanently discontinued from further trial treatment administration.	Any subject with a serious Grade 3 or any Grade 4 event will not be permitted to re-dose. Any subsequent redosing of nonserious Grade 3 events must be discussed an approved with the Medical Monitor.

Abbreviations: ECG=electrocardiogram; IV=intravenous; MB=myocardial band; NSAIDs=non-steroidal anti-inflammatory drugs; po=orally; WHO=World Health Organization.

6. STUDY DRUG DISCONTINUATION AND SUBJECT WITHDRAWAL FROM THE STUDY

6.1. Study Drug Discontinuation

An investigator may discontinue study drug or a subject may also choose to discontinue study drug at any time. Subjects who plan to discontinue early from the study drug or study should complete an Early Termination Visit 8 weeks after the last dose of study treatment.

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

1. Subject is noncompliant with the protocol
2. Subject is lost to follow-up
3. Subject withdraws consent
4. Subject has a serious or intolerable AE that, in the opinion of the investigator, requires withdrawal from the study treatment
5. Occurrence of an intercurrent illness that, in the opinion of the investigator, will affect assessments of clinical status or safety to a significant degree
6. Use of a nonpermitted concomitant medication
7. Pregnancy
8. Discretion of the investigator and Medical Monitor
9. Serum transaminases (ALT or AST) >3 × ULN and total bilirubin >2 × ULN without an alternative explanation
10. Anaphylaxis
11. Infusion-related or injection-related reaction despite adequate pre-medication for an initial occurrence of a moderate to severe infusion related reaction or if the subject experiences any of the following events: mucosal tissue involvement, airway compromise, or symptomatic hypotension with systolic BP <90 mm Hg measured in the supine position.

If a subject is withdrawn from study treatment due to an AE or a SAE, the subject will be followed up by the investigator until the abnormal parameter or symptom has resolved or stabilized (if applicable). Additional clinical work-up to further evaluate an AE or SAE may be recommended by the site investigator, in conjunction with the Medical Monitor, and the subject's treating ALS physician. It is recommended that the investigator consult with the Medical Monitor prior to removing the subject from study treatment for any reason except subject withdrawal of consent. Any subject may withdraw his or her consent at any time for any reason.

For all research subjects, the reason for permanent discontinuation of study drug must be recorded in the electronic eCRF. These data will be included in the trial database and reported.

6.2. Subject Withdrawal from the Study

Subjects may withdraw from the study at any time for any reason. An investigator should only withdraw a subject from the study if required to ensure the subject's safety even after discontinuation of study drug. The following is a list of possible reasons for subject withdrawal from the study:

1. Subject withdraws of consent
2. Subject is lost to follow-up
3. Subject is withdrawn from the study at the discretion of the investigator
4. Subject is withdrawn due to administrative or other reasons (eg, termination of the study by Alector)

All subjects who discontinue the study during and after the treatment phase, but before the final scheduled Study Completion Visit should be encouraged to return to the investigational site for an Early Termination Visit 8 weeks after the last dose of study treatment.

Reasonable attempts will be made by the investigator to obtain reasons for subject withdrawal (eg, 2 documented telephone calls on different days, followed by 1 registered letter). The reason for subject withdrawal from the study will be recorded on the eCRF.

6.3. Subject Lost to Follow-Up

A subject will be considered lost to follow-up if he or she fails to return for 3 consecutive scheduled study visits and is unable to be contacted by the study site staff.

The following actions must be taken and documented if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit within the study window and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to continue or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary, a certified letter to the subject’s last known mailing address or local equivalent methods). These contact attempts should be documented in the subject’s medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of "lost to follow-up".

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Efficacy Assessments

7.1.1. ALS Functional Rating Scale-Revised

The ALSFRS-R is a quickly administered (5-minute) ordinal rating scale used to determine the patient's assessment of their capability and independence in 12 functional activities (Cedarbaum 1999). All ALSFRS-R evaluators must be certified by the Northeast ALS Consortium (NEALS). Each functional activity is rated 0–4 for a total score that ranges from 0 to 48. Higher scores indicate better function. Initial validity in ALS patients was established by documenting that change in ALSFRS-R scores correlated with change in strength over time, was closely associated with quality-of-life measures, and predicted survival. The test-retest reliability is greater than 0.88 for all test items. The advantages of the ALSFRS-R are that all 12 functional activities are relevant to ALS, it is a sensitive and reliable tool for assessing activities of daily living function in those with ALS, and it is quickly administered. With appropriate training the ALSFRS-R can be administered with high inter-rater reliability and test-retest reliability.

When required due to pandemic-related restrictions, the ALSFRS-R can be administered via phone or web-based interface. The ALSFRS-R can be administered by phone with good inter-rater and test-retest reliability. The equivalency of phone versus in-person testing, and the equivalency of study subject versus caregiver responses have also been established. Additionally, the ALSFRS-R can also be obtained using a web-based interface with good concordance with in-person assessment.

7.1.2. Combined Assessment of Function and Survival

The Combined Assessment of Function and Survival (CAFS) (Berry 2013) evaluates treatment-dependent differences in disease progression as measured by survival time or change in function. CAFS ranks each pair of subjects' clinical outcomes based on survival time if evaluable or based on change in the ALSFRS-R total score if a comparison based on survival time is not evaluable. A subject's CAFS score is the sum of their ranking with respect to all other subjects. A higher CAFS score indicates a better outcome. CAFS scores are nonparametric and thus do not rely on statistical assumptions required for many of the standard techniques, such as linearity of disease progression or imputation of missing data.

7.1.3. Vital Capacity

Vital capacity will be determined using the upright SVC method. All evaluators performing SVC, must be NEALS certified*. The SVC will be measured using the study-approved* portable spirometer, and assessments will be performed using a face mask. A printout from the spirometer of all VC trials will be retained. Three VC trials are required for each testing session, however up to 5 trials may be performed if the variability between the highest and second highest VC is 10% or greater for the first 3 trials. Only the 3 best trials are recorded on the eCRF. The highest VC recorded is utilized for eligibility. At least 3 measurable VC trials must be completed to score VC for all visits after Screening. Predicted VC values and percent-predicted VC values will be calculated using the Quanjer Global Lung Initiative equations.

**Note: Exceptions to the requirement of NEALS evaluator certification and study-approved spirometer will be permitted if performed in a pulmonary function lab (including FEV1) during the Screening Visit as needed during the pandemic.*

7.1.4. Home Spirometry

Remote/home-based FVC will be measured with the MIR Spirobank Smart spirometer within 2 days of each in-person study visit. A mask will be provided to each subject for FVC assessment throughout the study. FVC assessments will be conducted remotely with the subject at home and connected with the evaluator via the Zephyrx Breathe Easy application (app) on the subject's mobile device and telemedicine platform (or phone, if telemedicine is not available). The app will enable video interaction between the subject and evaluator. The evaluator will observe the assessment and will provide instruction and coaching in real time. Three FVC trials are required for each testing session, however up to 5 trials may be performed if the variability between the highest and second highest VC is 10% or greater for the first 3 trials. The evaluator will print out the assessments via a secure online portal. At least 3 measurable FVC trials must be completed to score FVC for all visits after Screening. Predicted FVC values and percent-predicted FVC values will be calculated using the Quanjer Global Lung Initiative equations.

7.1.5. ALS Cognitive Behavioral Screen

The ALS Cognitive Behavioral Screen (ALS-CBS™) (Woolley 2010a) is a short measure of cognition and behavior in patients with ALS. The cognitive section includes commonly used elements of standard testing batteries, consisting of 8 tasks, with a total possible score of 20. It can be administered by a physician or other clinical care staff and takes approximately 5 minutes to complete.

The optional behavioral section (ALS Caregiver Behavioral Questionnaire) is composed of questions sensitive to organic brain changes. It consists of a set of questions that compare changes in personality and behavior since the onset of ALS, as well as yes/no questions about mood, pseudobulbar affect, and fatigue. It is completed by a caregiver, defined as an individual who lives with the subject and in the investigator's opinion has adequate knowledge of their daily activities and function. The caregiver completes the questionnaire during the same time that the subject completes the cognitive portion. The questionnaire typically takes about 2 minutes to complete. If a caregiver is not present during a visit, this section of the questionnaire will not be performed.

7.1.6. Digital Assessments

Voice samples and cognitive assessments will be collected once per week, using an app installed on either an android or iOS-based smartphone. Combined these estimates take about 10 minutes or less to complete.

For speech analysis, the app characterizes ambient noise, then asks the subject to perform a set of speaking tasks: reading 5 fixed sentences and 5 sentences chosen at random from a large sentence bank, repeating a consonant-vowel sequence (diadochokinetic rate), producing a sustained phonation, and counting on a single breath.

In cognitive evaluation the app asks the subject to view and listen to a story and repeat the story verbatim (story recall), describe a picture of a complex scene in their own words (complex

picture description), name as many items as possible within a provided category in 15 seconds (category naming), name objects as many shown objects as possible (object recall), describe their emotions associated with a picture provided (affect assessment), and rate their ability to communicate with others in various situations (social participation).

Voice signals and cognitive assessments are securely uploaded to a Health Insurance Portability and Accountability Act (HIPAA)-compliant web server, where an artificial intelligence (AI)-based analysis identifies relevant vocal attributes. Quality control (QC) of individual samples will occur by evaluation of voice records by trained personnel.

7.1.7. Training and Validation

All evaluators must be certified to perform the ALSFRS-R, ALS-CBS and VC assessments. Certification occurs via a formal evaluation of reliability and accuracy of performance of these measures. It is strongly preferred that a single evaluator performs all measures throughout the study, as much as possible.

7.2. Biofluid Collection and Sample Retention

All biosamples will be labeled with a unique identifying code. The code will not include any personal identification information. The code will be linked to a specific subject, visit, and sample by data entry of the code into the electronic data capture (EDC) system. 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 future use, if the subject agrees and provides consent separately. For subjects who have provided consent, these samples may be used for testing including the following: further evaluation of PD biomarkers (eg, associated with efficacy, AEs, or disease progression), further clarification or characterization of the disease, further evaluation of the study, and future testing not described in this protocol.

Specific instructions regarding the collection, processing, storage, and shipment of these samples will be provided in the central laboratory manual.

7.2.1. DNA Collection

All subjects will provide blood samples for repeat primed polymerase chain reaction (PCR) evaluation of the *C9orf72* repeat expansion and for DNA extraction for genotype determination of the rs5848 polymorphism at the Screening Visit. The same samples will be used for genotyping [redacted] polymorphisms and may be used for whole genome sequencing or DNA microarray analysis with the goal of, but limited to, identifying common and rare genetic variants that are predictive of response to study treatment, are associated with progression to a more severe disease state, are associated with susceptibility to developing AEs, or can increase the knowledge and understanding of disease biology.

7.2.2. Lumbar Puncture

LP will be performed to collect CSF as specified in the Schedule of Assessments. CSF will be collected at each visit for analysis of AL001 concentration and PD biomarkers.

Subjects may only undergo a LP if they have a coagulation panel and platelet count performed (using a central or local laboratory) within 4 weeks prior to the LP. If the laboratory results are abnormal and warrant repeat studies, they should be repeated within a week prior to the LP, and can be repeated at a local laboratory as needed. Lumbar puncture at Visit 8 is to be performed prior to study drug administration, and at approximately the same time of the day as the Screening LP. The LP is to be performed after pulmonary function testing and administration of the ALSFRS-R. For subjects who are rescreened, if an LP was previously completed as part of Screening and it is within 12 weeks of reconsenting, then a repeat LP is not necessary.

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

The investigator will discuss all potential LP risks to the subjects including:

- Local pain at injection site
- Reaction to anesthetic agents
- Bleeding at needle entrance site
- Infection at needle entrance site
- Post-LP low-pressure headache

Extensive experience with research LP in Alzheimer's disease reveals a very low incidence of complication, including the incidence of post-LP headache (Woolley 2010b). Fewer than 2.6% of patients in a memory disorder clinic developed post-LP headache, and only a single patient in a cohort of over 1,000 patients had a headache lasting more than 5 days (Woolley 2010b). No other local or generalized complications occurred.

Atraumatic needles will be used to further reduce the risk of post-LP headache (Quinn 2013). The procedure must be performed by the investigator or another licensed practitioner with experience and training in performing LPs, and must be listed on the site delegation log.

7.2.3. Pharmacokinetic Blood Sample Collection

Blood serum samples will be collected for assessment of serum concentrations of AL001 as specified in the Schedule of Assessments (Appendix 1) for the evaluation of AL001 concentrations.

7.2.4. Anti-Drug Antibodies

Blood serum samples will be collected for the determination of ADAs as specified in the Schedule of Assessments (Appendix 1). Samples should be collected prior to infusion.

Additional ADA samples should be collected in subjects with signs and symptoms of IRRs. In the event of an infusion reaction, blood samples should be obtained for serum PK and ADA assessments of AL001 or placebo, and the following laboratories should be drawn for assessment by the laboratory: CRP, ferritin, tryptase, and IL-6 (at 1 to 2 hours after the IRR, then again at 48–72 hours after the IRR). Where possible, clinical laboratory samples should be drawn at the site for the central laboratory; however, local laboratories may be utilized and results assessed for safety by the investigator.

7.2.5. Blood, Urine, and CSF Pharmacodynamic Assessments

As specified in the Schedule of Assessments (Appendix 1), blood, urine and CSF samples will be collected for the evaluation of PD biomarkers as follows:

Blood-Based Biomarkers:

- Plasma samples will be collected for evaluation of PGRN levels
- Plasma samples will be collected for evaluation of NfL levels
- Other exploratory PD biomarkers

CSF-Based Biomarkers:

- CSF samples collection will be evaluated for levels of PGRN and NfL
- Other exploratory PD biomarkers

Urine-Based Biomarkers:

- Urine samples will be collected for evaluation of [redacted] and creatinine
- Other exploratory PD biomarker

Timing and frequency of all PD biomarker assessments are presented in the Schedule of Assessments (Appendix 1).

7.2.6. Blood Biomarker Sample Collection

All subjects will provide blood samples for biomarker assessments at every study visit. Specific information on clinical laboratory, ADA, PK, PD biomarker, and pharmacogenomic sample collection, processing, storage, and shipment will be provided in separate manuals.

7.2.7. Urine Collection

Urine samples will be collected at all study visits starting at the Baseline Visit.

7.3. Safety and Other Assessments

7.3.1. Clinical Variables

In addition to the assessments listed above, the following clinical variables will be collected at the Screening Visit:

- Demographic data
- ALS disease history and genetic status
- Family history of ALS
- Medical history
- Concomitant medications

Assessment for changes in clinical variables will occur at every follow-up visit.

7.3.2. Vital Signs and Anthropometrics

Vital signs include weight in kilograms (kg), systolic and diastolic blood pressure in mmHg, pulse rate (radial artery)/minute, respiratory rate/minute, and temperature in °C. Height in centimeters (cm) will be measured and recorded at the Screening Visit (Visit 1) only. This one-time height measurement must be used throughout the duration of the study.

7.3.3. Clinical Safety Laboratory Tests

The laboratory tests to be performed for safety at Screening to determine eligibility and pre-infusion at every subsequent visit are listed in Table 2.

For any screening laboratory test value outside the reference range that the investigator considers clinically significant, repeat testing will be obtained through the central laboratory. For all other visits, any laboratory test value outside the reference range that the investigator considers clinically significant will be repeated either through a central or local laboratory, as deemed appropriate by the investigator.

All subjects will have clinical safety laboratory tests at the designated visits outlined in the Schedule of Assessments (Appendix 1). All laboratory samples will be analyzed at a central laboratory, with the exception of urine pregnancy testing or medically indicated laboratory tests to further assess an AE which will be done at local laboratories. The investigator may order additional local testing, if needed, to further assess an AE, or if there is any suspicion that a subject may be pregnant, throughout the course of the study.

Table 2: Clinical Safety Laboratory Tests

<table>
<tr><th>Chemistry</th><th>Coagulation</th><th>Hematology</th><th>Serology[5]</th></tr>
<tr><td rowspan="3">Total bilirubin
Direct bilirubin
Alkaline phosphatase
gammaGT
AST
ALT
LDH
Creatine kinase
Creatinine [1]
Urea
Uric acid
Cholesterol
HDL
LDL
Triglycerides
Total protein
Albumin
Glucose
Bicarbonate
Inorganic phosphate
Sodium
Potassium
Calcium
Chloride
Magnesium
Lipase</td><td>PT
INR
aPTT</td><td>HbA1c [5]
Leukocytes
Erythrocytes
Hemoglobin
Hematocrit
Thrombocytes (platelets)
MCV
MCH
MCHC

Partial automated differentiation:
Lymphocytes
Monocytes
Eosinophils
Basophils
Neutrophils [2]
ANC [2]</td><td>anti-HCV
anti-HIV
HIV antigen
HBsAg</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 [4] (sediment, erythrocytes, leukocytes, casts, crystals, epithelial cells, and bacteria)</td><td>Serum β-hCG or urine pregnancy test [3]</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; gamma GT=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 hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PT=prothrombin time.

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

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

[3] 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.

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

[5] Screening only.

7.3.4. 12-Lead ECG

12-lead ECGs will be obtained after the subject has been in the supine position for at least 5 minutes to determine eligibility and for safety as outlined in the Schedule of Assessments (Appendix 1). Tracings will be reviewed by an ECG reader and a copy of the tracings will be kept on site as part of the source documents. Additional ECG monitoring must be performed during the treatment period, if clinically indicated.

7.3.5. Physical Examination

Complete physical examinations will include evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, and gastrointestinal systems. Breast, genital, and rectal examinations are not required, unless warranted in the opinion of the examiner.

Record physical examination 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, unless the new or worsened event is related to the patient's ALS disease progression.

7.3.6. Neurological Examination

A complete neurologic examination will include the evaluation of consciousness, orientation, cranial nerves, motor and sensory system, coordination and gait, and reflexes.

Record neurological examination 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.

7.3.7. Columbia-Suicide Severity Rating Scale

Suicidality will be assessed with the C-SSRS. The C-SSRS involves a series of probing questions to inquire about possible suicidal thinking and behavior.

At the Baseline Visit, the C-SSRS baseline version will be administered. This version is used to assess suicidality over the subject's lifetime.

At all other visits, the Since Last Contact version of the C-SSRS will be administered. This version of the scale assesses suicidality since the subject's last visit.

If there is a positive response to question 4 or 5 on the severity of ideation subscale or any positive response on the suicidal behavior subscale of suicide attempt or suicidal ideation by the subject during the administration of the C-SSRS during the treatment period, the appropriately qualified clinician will be notified during the study visit to determine the appropriate actions required to ensure the subject's safety. The site must ensure that the subject is seen by a licensed physician (or other qualified individual as required by local institutional policy) before leaving the study site. The investigator will determine whether the subject should remain on study drug. Reference to the Clinical Triage Guidelines Using the C-SSRS can be found here https://cssrs.columbia.edu/wp-content/uploads/C-SSRStriageexampleguidelines.pdf.

It is recommended that a medically licensed physician, nurse, nurse practitioner, or physician assistant to assess suicidality with the C-SSRS. All evaluators must be certified to perform the C-SSRS. Certification is required prior to performing the C-SSRS.

8. ASSESSMENT OF SAFETY

The investigator is responsible for reporting all AEs and SAEs that are observed or reported during the study, from the time a subject provides consent until the completion of their study participation, regardless of their relationship to study treatment or their clinical significance.

The investigator's assessment of the relationship of an AE or SAE to study treatment is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE/SAE, and the event is not a sign or symptom of another reported AE/SAE, the observation should be reported as an AE/SAE. All AEs/SAEs that are observed or reported during the study, from the time a prospective participant provides consent until the completion of their study participation, must be reported, regardless of their relationship to study treatment or their clinical significance.

8.1. Definition of Adverse Event

Adverse events are any untoward medical occurrence in a subject enrolled into this study, including side effects, injury, toxicity, sensitivity reaction, intercurrent illnesses, clinically significant physical exam signs, or sudden death, whether or not it is considered related to the study treatment. Subjects will be instructed to contact the investigator at any time after informed consent if any symptoms develop. Subjects will be instructed to report all AEs to the investigator. All AEs must be appropriately documented in the subject's original source documents and on the eCRFs. Investigators should report the diagnosis rather than list symptoms, whenever possible.

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

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

An AE does not include the following:

- Elective medical or surgical procedures planned prior to the start of study treatment (eg, hip replacement surgery) that did not result from a worsening of a previous condition (ie, prior to signing informed consent). *Note:* Any serious procedural complication or hospital-emergent conditions (eg, nosocomial infection) would be reported as an SAE.
- Any medical condition or clinically significant laboratory abnormality that has an onset date before the consent form is signed, and that is not related to a protocol-associated procedure, is not an AE. Such conditions are considered to be pre-existing and should be documented on the medical history eCRF. A pre-existing condition should be reported as an AE only if its frequency, intensity, or symptoms worsen during the course of the study.
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for study treatment administration per institutional guidelines, elective surgery, social and/or convenience admissions).

- Overdose without adverse event.
- Disease progression within expected parameters for the study population is not considered an AE. See Section 8.3 for Protocol Specific Disease Progression Adverse Event and Serious Adverse Event Reporting Requirements.

8.2. Definition of Serious Adverse Event

An SAE is defined as any adverse event that fulfill one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization:
  - Social hospitalization, defined as inadequate family support or care at the subject's primary residence resulting in subject hospitalization, will not be considered an SAE
  - Any pre-planned hospitalization for a condition that did not worsen while the subject was on study is not considered an SAE; however, any events that cause prolongation of the hospitalization would be captured as such. Similarly, elective surgical procedures performed during the study that are intended to treat pre-existing conditions are not considered adverse events.
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Important medical events that may not meet one of the above criteria could be considered a SAE by the investigator when, based upon appropriate medical judgment, they are considered clinically significant and may jeopardize the subject, or may require medical or surgical intervention to prevent one of the outcomes listed above.

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

8.3. Protocol Specific Disease Progression Adverse Event and Serious Adverse Event Reporting Requirements

Disease progression in this study is measured via the ALSFRS-R and VC. 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.

8.4. Definition of Clinical Laboratory Abnormalities and Other Abnormal Assessments as AE/SAE

Abnormal laboratory findings (hematology, coagulation, chemistry, and urinalysis) or other abnormal assessments (ECG, vital signs) per se are not reported as AEs. However, those abnormal findings that are deemed clinically significant or are associated with signs and/or symptoms must be recorded as AEs if they meet the definition of an AE (or recorded as an SAE if they meet the criteria of being serious) as previously described. Clinically significant abnormal laboratory or other abnormal findings that are detected after consent or that are present at baseline and worsen after consent are included as AEs (and SAEs if serious).

The investigator should exercise medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. Usually, the abnormality should be associated with a clinically evident sign or symptom or be likely to result in an evident sign or symptom in the near term, to be considered clinically significant.

A clinically significant laboratory abnormality in the absence of clinical symptoms may jeopardize the subject and may require intervention to prevent immediate consequences. For example, a markedly low serum glucose concentration may not be accompanied by coma or convulsions, yet be of a magnitude to require glucose administration to prevent such sequelae.

8.5. Assessment of Adverse Events

8.5.1. Assessment of Adverse Event/Serious Adverse Event Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the subject's daily activities. Severity will be graded according to the World Health Organization (WHO) Toxicity Grading Scale, March 2020 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 subject 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 or therapy required.
3	Severe*	Marked limitation in activity; medical intervention or therapy required; hospitalizations possible.
4	Life-Threatening	The subject is at risk of death due to the AE as it occurred. This does not refer to an AE that hypothetically might have caused death if it were more severe.
5	Death	Any AE where the outcome is death.

Abbreviation: AE=adverse event.
*Note that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. AEs characterized as intermittent do not require documentation of onset and duration of each episode. When the 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 (ie, as having distinct onset dates).

8.5.2. Assessment of Adverse Event/Serious Adverse Event Causality

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

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

The investigator should assess causality by answering either "related" or "not related" to the question "Is there a reasonable possibility that the event may have been caused by the study treatment?" The following factors may be used in consideration of causality assessment:

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

8.6. Recording of Adverse Events

8.6.1. Eliciting and Documenting the Adverse Events

At every study visit, subjects 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 (eg, falls), used any new medications, or changed concomitant medication regimens (prescription drugs, herbal products, vitamins, minerals, vaccines, topical medications, and over-the-counter medications).

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

- Is confirmed and the investigator considers it clinically significant

- Requires a subject to discontinue study drug
- Requires a subject to receive treatment

Abnormal laboratory test values or investigational findings reported as AEs or SAEs should be followed until recovered/resolved, until stable, subject withdrawal of consent, lost to follow-up, or death, whichever comes first.

8.6.2. Recording the Action Taken with Investigational Products in Response to Adverse Events/Serious Adverse Events

Should the investigator need to alter the administration of the investigational product from the procedure described in the protocol in response to an AE/SAE, then the action taken will be recorded on the AE eCRF page as one of the following options:

- Dose reduced
- Dose interrupted
- Dose withdrawn
- Not applicable
- Unknown

8.6.3. Recording the Outcome and Follow-Up of Subjects Reporting an Adverse Event/Serious Adverse Event

Outcome of an AE/SAE will be recorded on the AE eCRF as follows:

- Recovered/Resolved
- Recovered/Resolved with Sequelae (with sequelae being a condition that is the consequence of the reported event, and not the event in a lower grade/ severity)
- Not Recovered/Not Resolved
- Fatal
- Unknown (or subject lost to follow-up after 4 attempts to contact over a period of 30 days since last information has been received).

8.7. Reporting Adverse Events

8.7.1. Adverse Event and Serious Adverse Event Reporting

All AEs and SAEs must be recorded and reported, regardless of cause or relationship, that occur after the subject signs informed consent through the end of study (EOS) visit. After this period, Alector should be notified if the investigator becomes aware of any SAE that is believed to be related to prior study drug treatment. Alector will follow any unresolved AEs and/or SAEs through satisfactory clinical resolution. Additionally, SAEs considered related to study treatment that occur at any time should be reported to Alector by the investigator.

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

of becoming aware of the event or aware of new information relating to the event. In the event that the EDC system is not available, a paper SAE Report Form should be used and emailed to drugsafety@alector.com, according to the instructions provided in the Study-Specific Regulatory Binder.

SAE information to be collected includes the following:

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

The Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or later will be used by Alector to code all AEs.

If additional visits are required before EOS, the subject will be asked to return to the investigational site for further follow-up. As additional information becomes available, such as hospital discharge notes and subject 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 this section), 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 SUSARs).

8.8. Safety Monitoring

Safety will be continuously reviewed by a Medical Monitor in consultation with the study investigators. Adverse events will be reported to the Medical Monitor from the study EDC system at regular intervals throughout the study, and in real time when SAEs occur or when questions arise. The Medical Monitor will have the authority to recommend study discontinuation or modification based on medical concerns, including AE or SAE profiles.

For medical emergencies, contact:

Study Medical Monitor
Margherita Torti, MD [redacted]

The Medical Monitor will review AE reports, compiled by Data Management, as described in the Safety Monitoring Plan. The Medical Monitor will review blinded study data on enrollment, abnormal laboratory results and protocol deviations. These reports will collectively be known as the Medical Monitoring Report.

Alector will be responsible for notifying the applicable regulatory agencies of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, Alector must notify the applicable regulatory agencies and all participating investigators in an Investigational New Drug safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after Alector determines that the information qualifies for reporting.

8.9. Follow-Up of AEs and SAEs

All AEs and SAEs that are deemed related to the investigational product must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject dies or is lost to follow-up. The investigator is responsible for ensuring that follow-up includes any supplemental investigations that may be indicated to elucidate as completely as practical the nature and/or causality of the AE/SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Alector may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a subject dies during participation in the study or during a recognized follow-up period, the sponsor should be provided with a copy of any post-mortem findings, including histopathology.

8.10. General Safety Monitoring

8.10.1. Special Situations

Special situations are non-standard medical conditions that provide valuable information about an investigational product and therefore should be reported. All special situations associated with an AE or SAE should be recorded in the EDC system in the applicable AE/SAE eCRF within 24 hours of becoming aware of the special situation. Special situations are defined as below:

Overdose: This refers to the administration of a quantity of an investigational product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information. Clinical judgement should always be applied.

Misuse: This refers to situations where the investigational product 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 an investigational product, 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. 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 investigational product for human use as a result of one's occupation.

8.10.1.1. Pregnancy

Female subjects must be instructed to discontinue all study treatments and inform the investigator immediately if they become pregnant during the study. The investigator must report any pregnancy within 24 hours of becoming aware of it using the Pregnancy Report form.

The investigational site should email the Pregnancy Report Form to drugsafety@alector.com, according to the instructions provided in the Study-Specific Regulatory Binder. 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 subjects or in the sexual partners of male subjects from the time the subject is first exposed to the study treatment until 10 weeks after the last dose of study drug. Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study, and considered by the investigator as possibly related to the study treatment, must be promptly reported to Alector.

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

8.10.1.2. Breastfeeding

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

8.10.1.3. Reportable Diseases

In the case a subject has or manifests any clinical signs characteristic of a reportable disease or condition, eg, HIV, tuberculosis, SARS, COVID-19, it is the responsibility of the investigator to notify Alector after becoming aware of the information.

9. STATISTICAL CONSIDERATIONS

9.1. Safety

Using the calculation power = $1-(1-p)^n$, where p is probability of an event and n is the number of subjects in a treatment arm, with 30 subjects exposed to the treatment (45 total study subjects randomized 2:1, treatment:placebo), there will be a >80% chance of seeing at least one occurrence of any SAE resulting from treatment with AL001 for which the expected frequency is at least 5.2% of exposed subjects, a rate of 8.5 events per 100-patient years, assuming uniform risk over 32 weeks.

9.2. Populations for Analyses

Full Data: All subjects who receive at least one dose of AL001 or placebo will be included in the analysis datasets for safety, tolerability, immunogenicity, clinical outcomes, and PD.

PK Data: All subjects who receive at least one dose of AL001 or placebo, and from whom at least one serum or CSF sample is analyzed for AL001 concentration, will be included in PK analyses.

9.3. Statistical Analyses

9.3.1. General Approach

Details of the planned analyses will be specified in a separate statistical analysis plan (SAP). As this is an exploratory study, no adjustments for multiplicity will be made. Data from all centers will be pooled for analysis purposes.

9.3.2. Analysis of the Primary Pharmacokinetic Endpoints

Pharmacokinetic measures will be summarized using descriptive statistics and AL001 concentrations in serum and CSF will be summarized using descriptive statistics by treatment group, visit, and time point.

9.3.3. Analysis of the Primary Pharmacodynamic Endpoints

Plasma and CSF levels of PGRN will be summarized using descriptive statistics for each treatment group at each visit. [redacted]

9.3.4. Analysis of the Primary Immunogenicity Endpoint

Immunogenicity test results for ADA to AL001 will be summarized using descriptive statistics by treatment group and visit.

9.3.5. Analysis of the Secondary Endpoint(s)

Neurofilament light levels in the blood and CSF will be summarized using descriptive statistics by treatment group and visit and analyzed using the same approach as outlined for PGRN levels.

9.3.6. Safety Analyses

9.3.6.1. Safety

Safety will be assessed by the occurrence of TEAEs, treatment-emergent SAEs, and treatment-emergent clinically significant abnormalities in clinical and laboratory values. AEs will be coded to system organ class and preferred term using the MedDRA Version 22.0 or later and summarized as counts of events and proportions of subjects experiencing a given type of event, by treatment group.

Summaries by severity, relationship to the study intervention, action taken with respect to study intervention, and outcome of all TEAEs will also be provided, by treatment group.

9.3.6.2. Tolerability

Tolerability will be defined as the percentage of subjects who complete the trial without treatment-emergent AEs leading to treatment discontinuation. Exact confidence bounds on the estimated percentage within each treatment group and the risk difference will be reported.

9.3.7. Baseline Descriptive Statistics

Baseline characteristics including age, sex, weight, site of symptom onset, time from symptom onset to diagnosis, time from symptom onset to first AL001 infusion, riluzole use, edaravone use, noninvasive ventilation use, forced vital capacity prior to first AL001 infusion, and measures of disease burden (ALSFRS-R, ALS-CBS) prior to first AL001 infusion will be summarized using appropriate descriptive statistics.

9.3.8. Planned Interim Analyses

There are no planned interim analyses for efficacy.

9.3.9. Sub-Group Analyses

Subgroups defined by the SNPs rs5848, [redacted] will be tested for pharmacogenomics effects on PD biomarkers. For each SNP, [redacted]

Subgroup-specific effects of AL001 will also be tested for subgroups defined by baseline use of edaravone and baseline use of riluzole using the same extension of the model.

9.3.10. Tabulation of Individual Subject Data

Individual subject data will be listed by measure and visit.

9.3.11. Exploratory Analyses

Exploratory outcomes will be summarized using appropriate descriptive statistics. Outcomes for which a consistent rate of progression is expected over 28 weeks, [redacted]

[redacted]

10. REGULATORY, ETHICAL, AND STUDY OVERSIGHT

10.1. Informed Consent Process

A written informed consent in compliance with US Title 21 CFR Part 50 and any other applicable regulatory authority regulations shall be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. 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 Institutional Review Board (IRB) submission. Once reviewed, the consent will be submitted by the investigator to the IRB for review and approval before the start of the study. If the informed consent form (ICF) is revised during the course of the study, active participating subjects may need to sign the revised form as determined by the IRB and/or Sponsor.

Before recruitment and enrollment, each prospective subject and caregiver (if applicable) will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing the ICF. The subject's caregiver, if applicable, will also be asked to give consent to participate in the optional caregiver portion of the ALS-CBS by signing an ICF.

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

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the subject, or caregiver (if applicable).

10.2. Study Suspension or 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 subject completes the last visit (includes follow-up visit).

10.3. Confidentiality and Privacy

Subject confidentiality and privacy are strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB/Independent Ethics Committee (IEC), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and

pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/IEC, Institutional policies, or sponsor requirements.

Data generated by this study must be available for inspection by representatives of the United States (US) FDA, the Office for Human Research Protections (OHRP), the sponsor, all pertinent national and local health and regulatory authorities, the Coordinating Center or their representative, study monitoring personnel, and the central IRB.

10.4. Future Use of Stored Specimens and Data

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 future use, if the subject agrees and provides consent. For subjects who have provided consent, the samples may be used for testing including the following: further evaluation of PD biomarkers (eg, 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 (eg, PD biomarker or diagnostic assays), and for future testing not described in this protocol.

10.5. Safety Oversight

Safety oversight will be under the direction of the Alector Medical Monitor.

An iDMC for the AL001-ALS-201 study will be established by the Sponsor to review accumulating study data in order to monitor the safety of all participants on an ongoing basis. No Alector employee or investigator involved in the AL001 clinical studies will be a member of the iDMC or participate in closed iDMC sessions; however, representatives from Alector may attend the open meeting sessions and will be able to provide additional information, as requested.

The iDMC will review the progress of the study and perform interim reviews to evaluate potential safety and tolerability issues for AL001.

The iDMC will act in an advisory capacity to the sponsor. The iDMC responsibilities will be detailed in an iDMC charter.

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

10.6. Clinical Monitoring

Study monitors will review source documentation, ICF, and the clinical facilities to ensure the study is conducted in accordance with the study protocol and compliance with ICH/GCP and regulatory guidelines. Investigators are responsible for allowing access to all source documents and medical records related to the subject's participation in the study. Monitoring visits will occur at defined intervals per the Clinical Monitoring Plan (CMP). Study monitor(s) will identify study noncompliance and if appropriate, the study monitor(s) will assist the site with developing

a corrective and preventative action plan. All significant noncompliance will be communicated to the Sponsor.

Specific monitoring activities, including remote data verification, will be outlined in the CMP.

10.6.1. Monitoring Report

The Study Monitors will provide monitoring reports to the Study Team and, will provide reports of protocol compliance to the Study Sponsor and other applicable parties as detailed in the CMP.

10.7. Quality Assurance and Quality Control

Protocol procedures are reviewed with the investigator and associated personnel prior to the study to ensure the accuracy and reliability of data. Each investigator must adhere to the protocol detailed in this document and agree that any changes to the protocol must be approved by the IRB prior to implementing the change unless it is to address immediate subject safety. No prospective protocol waivers will be issued or approved/pre-approved.

Quality control procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (eg, GLP, GMP).

The investigational site will provide direct access to all trial related sites (including pharmacy), source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. Specifics regarding pharmacy visits will be outlined in the Pharmacy Manual.

The investigational product and associated documentation will be monitored during interim, remote, and final on-site visits. The unblinded clinical research associate (CRA) will review the investigational product inventory on-site and associated pharmacy inventory documentation during on-site visits; this also includes shipping receipts, temperature logs, and the study storage area. After all subjects at the site have completed the treatment phase of the study, any unused investigational product will be destroyed in accordance with each institution’s investigational product destruction policy, following the monitor’s authorization of destruction. It is acceptable for the unblinded CRA to verify and authorize all returned study investigational product for destruction during interim monitoring visits if permitted by the site’s investigational product destruction policy. A copy of each site’s Drug Destruction SOP or policy shall be provided to the Project Manager and filed in the Pharmacy Binder. All pharmacy documentation should be kept on file at the site. A detailed description of investigational product storage, accountability, as well as resupply and destruction, can be found in the Pharmacy Manual.

10.8. Data Handling and Record Keeping

10.8.1. Role of Data Management

Data management is the development, execution and supervision of plans, policies, programs, and practices that control, protect, deliver, and enhance the value of data and information assets. The EDC system will facilitate the collection, management, monitoring, and reporting of study data.

10.8.2. Data Collection

Site personnel will collect data onto paper source documents as appropriate and into electronic source documents (eg, voice sample data). Values from paper source documents will be transcribed into the corresponding eCRFs in the EDC system by site personnel; electronically captured data will be transmitted to their respective vendors for consolidation and reconciliation with the study EDC system. Clinical sites will be monitored to ensure compliance with the study protocol, data management requirements, and GCP.

10.8.3. Data Entry and Edit Checks

Site personnel are instructed to enter collected data into the EDC system within 5 days of a visit. Please note: SAEs must be entered into the EDC system and reported to the Coordination Center (CC) within 24 hours of site awareness of the SAE. Data collection is the responsibility of the staff at the site under the supervision of the investigator as specified in the delegation log for that site. During the study, the investigator must maintain complete and accurate documentation for the study.

To ensure accuracy and completeness of the data set, logic and range checks as well as in-form rules will be built into the EDC system, and electronic queries will be created to track potential data issues. The sites will only have access to the queries concerning their own subjects.

10.8.4. Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the EDC a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.9. Study Records Retention

US FDA regulations (21 CFR 312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drugs, including CRFs (if applicable), consent forms, laboratory test results, and medical inventory records, must be retained by the investigator for two years after marketing application approval. If no application is filed, these records must be kept for two years after the investigation is discontinued and the US FDA and the applicable national and local health authorities are notified. The CC or their representative will notify the investigators of these events.

10.10. Protocol Deviations

The investigator or designee must document and explain in the subject'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 subjects 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 subject, investigator, or Alector (or designee) fails to adhere to protocol requirements. Major protocol deviations are the ones that affect the subjects' safety or the primary endpoint (safety). Major protocol deviations for this study include, but are not limited to, the following:

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

10.11. Publication and Data Sharing Policy

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.

10.12. Conflict of Interest Policy

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

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

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership at Massachusetts General Hospital (MGH), in conjunction with Neurological Clinical Research Institute (NCRI), has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Visit Name[26]	Visit 1 Screening[1]	Visit 2 Baseline[2]	Visit 3[3]	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9[4]	Visit 10 Study Completion Visit	Early Termination Visit[25]
Visit Timing (Visit Window)	Week -3 to Day 0	Week 0 Day 0	Week 4 (± 7 days)	Week 8 (± 7 days)	Week 12 (± 7 days)	Week 16 (± 7 days)	Week 20 (± 7 days)	Week 24 (± 7 days)	Week 28 (±7 days)	Week 32 (± 7 days)	
Written Informed Consent	X										
Inclusion/Exclusion Review	X	X									
Medical History/ Demographics	X										
ALS Diagnosis History	X										
Physical Examination	X	X	X	X	X	X	X	X		X	X
Neurological Examination	X	X	X	X	X	X	X	X		X	X
Vital Signs[5]	X	X	X	X	X	X	X	X		X	X
Height & Weight[6]	X	X	X	X	X	X	X	X		X	X
12-Lead ECG[7]	X	X			X			X			X
Screening Laboratory Tests[8]	X										
Safety Laboratory Tests[9]		X	X	X	X	X	X	X		X	X
Coagulation[10]	X						X				
Whole Blood Sample for Targeted Genomic Variants	X										
Serum PK Samples[11]		X	X	X	X[11]	X	X	X		X	X
Biomarker Samples[12]	X	X	X	X	X	X	X	X		X	X
Serum ADA Samples[13]		X	X	X	X	X	X	X		X	X
Pregnancy Test[14]	X	X	X	X	X	X	X	X		X	X
Lumbar Puncture[15]	X							X			X[24]
ALSFRS-R[16]		X	X	X	X	X	X	X	X	X	X
Pulmonary Function Testing[17]	X	X	X	X	X	X	X	X		X	X
ALS-CBS[18]		X					X			X	X
Suicide Assessment (C-SSRS)[19]		X	X	X	X	X	X	X		X	X
Digital Monitoring[20]		X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Review[21]	X	X	X	X	X	X	X	X	X	X	X
Randomization		X									
AL001/Placebo Intravenous Infusion[22]		X[23]	X	X	X	X	X	X			

Abbreviations: ADA=anti-drug antibody; AE=adverse event; ALS=amyotrophic lateral sclerosis; ALS-CBS=ALS Cognitive Behavioral Screen; ALSFRS-R=ALS Functional Rating Scale-Revised; aPTT=activated prothromboplastin time; CBC=complete blood count; CRP=C-reactive protein; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; FVC=forced vital capacity; IL-6=interleukin 6; INR=international normalized ratio; IRR=infusion-related reaction; LP=lumbar puncture; PK=pharmacokinetic; PFT=Pulmonary Function Testing; PT=prothrombin time; SVC=slow vital capacity; VC=vital capacity.

[1] Screening procedures must be completed within 21 days prior to the Baseline Visit.

[2] If necessary, the Baseline Visit may be conducted over 2 consecutive days. The following procedures may be performed on the first day of the split visit: inclusion/exclusion review, weight, randomization, physical examination, neurological examination, ALSFRS-R, ALS-CBS, pulmonary function test, C-SSRS, and digital monitoring. The following must be completed on the second day of the split visit: collection of safety laboratory samples, serum PK samples (pre-infusion and post-infusion as outlined in footnote 11), biomarker samples, serum ADA samples, serum pregnancy test, vital signs, and 12-lead ECG. Study drug infusion must always be on the second day of a split Baseline Visit. Concomitant medication and AE review should be completed on each day.

[3] After the Baseline Visit, visit procedures at any subsequent visit may be completed over the course of a 48-hour period; however, the following must be completed on the day of study drug administration: collection of safety laboratory samples, serum PK samples (except for 24-hour post infusion PK at Visit 5, see footnote 11), biomarker samples, serum ADA samples, pregnancy test (if applicable), vital signs, and 12-lead ECG. The lumbar puncture must be performed prior to infusion for all visits where an LP is required (as outlined in footnote 15).

[4] Visit 9 will be a telephone visit and will include the ALSFRS-R, a review of concomitant medications, and a review of adverse events.

[5] Vital signs include systolic and diastolic pressure in mmHg, respiratory rate/minute, heart rate/minute and temperature. For Visits 2-8 vital signs will be performed pre-dose and within 15 minutes after the end of the infusion.

[6] Height measured at Screening Visit only. Weight to be performed prior to infusion for Visits 2-8.

[7] 12-lead ECGs will be obtained after the subject has been in the supine position for at least 5 minutes. Additional ECG monitoring must be performed during the treatment period, if clinically indicated. On dosing days, the ECG will be obtained within 60 minutes after the end of infusion.

[8] Screening laboratory tests include hematology (CBC with differential), complete chemistry panel (to include liver function tests), hepatitis B surface antigen, hepatitis C viral antibodies, HIV-1/2 antibodies and antigen, urinalysis. Serum pregnancy test will be performed in women of childbearing potential.

[9] Safety laboratory tests will be performed pre-infusion and include hematology (CBC with differential), complete chemistry panel (to include liver function tests), and urinalysis. Urine pregnancy test will be performed in women of childbearing potential.

[10] A coagulation panel including PT/INR, aPTT is to be performed at Screening and Visit 7.

[11] Serum PK samples will be drawn pre-infusion on the day of the infusion visit and within 15 minutes after the end of infusion (including the line flush). Additional serum PK samples will be collected at Visit 5 at 3 hours (± 90 minutes) post end of infusion. Subjects will also be required to return to the study site for the Visit 5 at 24 hours (±6 hours) post end of infusion for additional serum PK samples.

[12] Biomarker samples include plasma and urine at Visits 2-10 and Early Termination. At the Screening Visit, only plasma will be collected.

[13] Blood serum samples will be collected prior to infusion for determination of ADA. In the event of an infusion reaction, blood samples should be obtained for serum PK and ADA assessments of AL001 or placebo, and the following assessments should be performed: CRP, ferritin, tryptase, and IL-6 (at 1 to 2 hours after the IRR, then again at 48-72 hours after the IRR). Where possible, clinical laboratory samples should be drawn at the site for the central laboratory; however, local laboratories may be utilized and results assessed for safety by the investigator.

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

[15] Subjects may only undergo a LP if they have a coagulation panel and platelet count performed (using a central or local laboratory) within 4 weeks prior to the LP. If the laboratory results are abnormal and warrant repeat studies, they should be repeated within a week prior to the LP, and can be repeated at a local laboratory as needed. Lumbar puncture at Visit 8 is to be performed prior to study drug administration, and at approximately the same time of the day as the

Screening LP. The LP is to be performed after pulmonary function testing and administration of the ALSFRS-R. For subjects who are rescreened, if a LP was previously completed as part of Screening and is within 12 weeks of reconsenting, then a repeat LP is not necessary.

[16] ALS Functional Rating Scale-Revised.

[17] Pulmonary function testing (PFT) includes slow vital capacity (SVC) at in-clinic study visits and FVC and forced expiratory volume in one second (FEV1) when conducted in a PFT lab. In addition to this in-clinic assessment, home spirometry will be performed with virtual coaching by study staff within 2 days of each in-clinic study visit. The initial home spirometry assessment will be performed in clinic with study staff at the Baseline visit with retest at home with virtual coaching by study staff within 2 days after the Baseline visit.

[18] ALS Cognitive Behavioral Scale.

[19] C-SSRS Baseline Version to be completed at Baseline Visit only. C-SSRS Since Last Contact version to be completed at all other visits.

[20] Digital monitoring to occur approximately weekly. Subjects will undergo set up of digital monitoring smartphone application and initial use with study staff during the Baseline Visit. All subsequent weekly digital monitoring should occur at home and before noon, if possible, to minimize the potential effects of fatigue. At every in-person visit after Baseline study staff will check-in on subject use and app-related questions.

[21] Adverse events that occur AFTER signing consent form will be recorded.

[22] AL001 should be infused over 60 minutes, with a 60 minutes observation period following infusion completion for the first 2 infusions (30 minutes for subsequent infusions). In the event of an infusion-related reaction, blood will be drawn for PK serum and ADA assessment of AL001 or placebo; the following laboratory tests should be drawn: CRP, ferritin, tryptase, and IL-6 (at 1 to 2 hours after the IRR, then again at 48-72 hours after the IRR). Where possible, clinical laboratory samples should be drawn at the site for the central laboratory; however, local laboratories may be utilized and results assessed for safety by the investigator.

[23] Administer first dose of study drug AFTER Baseline Visit procedures are completed.

[24] Subjects may only undergo a LP if they have a coagulation panel and platelet count performed (using a central or local laboratory) within 4 weeks prior to the LP. If the laboratory results are abnormal and warrant repeat studies, they should be repeated within a week prior to the LP, and can be repeated at a local laboratory as needed. Lumbar puncture is to be performed at approximately the same time of the day as the Screening LP. The LP is to be performed after pulmonary function testing and administration of the ALSFRS-R.

[25] The Early Termination Visit should occur 8 weeks after the last dose of study treatment.

[26] If the assessment cannot be performed at the scheduled visit due to the COVID-19 pandemic, the assessments may be performed remotely or at a future on-site visit with approval from the Medical Monitor. Refer to Appendix 2 for additional details on trial adaptations due to COVID.

APPENDIX 2. ADAPTATION OF TRIAL PROTOCOL DURING THE 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-ALS-201 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 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 Adaptations

The implementation of adaptations to study visits and procedures 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/travel, 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 Assessments. This is due to reduced time for on-site visits, limited or no availability of some services on site, and 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
- C-SSRS
- Study drug administration

Remote Essential Assessments

If patients or raters are not able to come to the study site 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
- ALSFRS-R
- C-SSRS

On-Site Assessments that Cannot be Completed at Scheduled Visits

In the event that a scheduled assessment cannot be completed at the site, eg, limited availability/restriction of equipment, patient has 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 rescheduled assessments.

COVID-19 Reporting

In the event that 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.

Remote Consent

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

Remote Source Document Verification

Remote source document verification will be employed in the following circumstances:

- International law, regulatory authorities, and the IRB/IEC permit this process and on-site 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 (eg, 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, if required per local regulations:

- The site CRA will complete a confidentiality agreement committing to the following:
  - To securely destroy any copies of documents received from sites (paper or electronic)
  - Not to take any recording during video access
- Remote SDV will only be completed for subjects who have consented to allow access to their health records remotely

Home Visits

To allow for collection of safety and protocol assessment data, and continuity of study drug administration, a home health service may be employed. A home visit for the purposes of this appendix is a visit to a patient's home or an alternative convenient location, such as an alternate site.

In event of home visits being employed, appropriate regulatory and ethics approval will be obtained prior to implementation.

The following **MUST** be completed as on-site visits:

- Screening Visit
- Randomization Visit
- First study drug infusion
- Second study drug infusion

All other visits may be completed as home visits.

Document Approvals

Approval Task Verdict: Approve	Brian Mangal, ([redacted]) SME Approval 11-Feb-2022 17:03:46 GMT+0000

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