STATISTICAL ANALYSIS PLAN
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

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ALECTOR APPROVAL SIGNATURE PAGE

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LIST OF ABBREVIATIONS

aPTT	activated partial thromboplastin time
AE	adverse event/adverse experience
ALP	alkaline phosphatase
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase
AST	aspartate aminotransferase
C9ALS	*C9orf72*-associated amyotrophic lateral sclerosis
CRP	C-Reactive Protein
CSF	cerebral spinal fluid
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
GCP	Good Clinical Practice
INR	international normalized ratio
IRR	infusion-related reaction
IV	intravenous
kg	kilogram
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic
PGRN	progranulin
PK	pharmacokinetic
PT	preferred term/prothrombin time
sCSR	Synoptic clinical study report
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TDP-43	TAR DNA-binding protein 43
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

Study AL001-ALS-201 titled "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" was halted early after 5 participants were enrolled. The study was not halted for safety reasons. Due to the limited number of patients enrolled, a synoptic clinical study report (sCSR) will be produced.

This statistical analysis plan (SAP) provides a brief description of the planned analysis and reporting to support the development of the sCSR. This SAP is based on Protocol version 3.0 dated 11 February 2022.

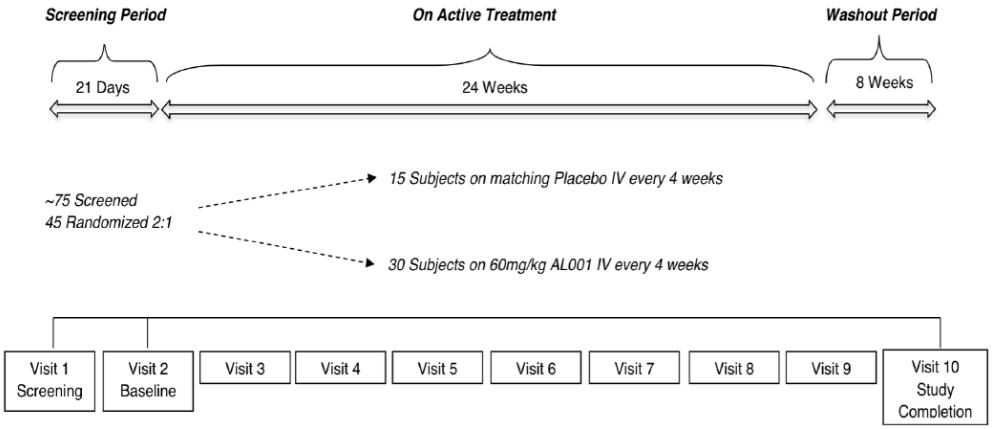
2. STUDY DESIGN

2.1. Design Overview

This is a Phase 2, multicenter, randomized clinical trial evaluating the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of AL001 compared to placebo in 5 adults with *C9orf72*-associated Amyotrophic Lateral Sclerosis (C9ALS). AL001 is hypothesized to protect motor neurons by increasing extracellular progranulin (PGRN) levels and thereby reducing TAR DNA-binding protein 43 (TDP-43) pathology in amyotrophic lateral sclerosis (ALS). The trial has been designed to confirm elevation of PGRN and accumulation of AL001 in cerebral spinal fluid (CSF) and to provide proof-of-mechanism target engagement in preparation for a larger trial testing the clinical efficacy of AL001 in 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). Day 0 is defined as the baseline, the first date of study drug administration.

Subjects will be randomly assigned to receive either standard of care + AL001 or standard of care + placebo in a 2:1 ratio with stratification by rs5848 genotype (3 levels: CC, CT, and TT). Randomization will use each stratum specific computer-generated permuted block randomization schedule with an undisclosed block size. Seven doses of AL001 60 mg/kg or matching placebo are planned to be administered via intravenous (IV) infusion every 4 weeks for 24 weeks (Visit 2 through Visit 8). Overview of Study Schema is shown below:



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 procedures shown in the Schedule of Assessments. 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.

3. STATISTICAL METHODS

3.1. General Considerations

No formal statistical analyses are planned. Key data will be provided in listings. All listings will be produced at the completion of the study for the sCSR using SAS® software version 9.4.

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 for system organ class (SOC) and preferred term (PT). Severity AEs 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[1]	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.

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

Relatedness of each AE to the study treatment is assessed by the investigator as 'Related' or 'Not Related'.

3.1.1. Baseline Definition

Unless otherwise specified, baseline value of a variable is defined as the last non-missing value prior to the first study treatment (Day 0).

3.2. Analysis Populations

3.2.1. Safety Analysis Set

All subjects who receive at least one dose of AL001 or placebo will be included in the Safety Analysis Set.

4. LISTINGS

All listings will use the Safety Analysis Set.

4.1. Subject Disposition, Demographics

Subject demographics and rs5848 genotype (age, sex, ethnicity, race, screening weight, genotype) and disposition (study drug completion status, and study completion status) will be listed.

4.2. Exposure to Study Drug

Doses of AL001 or placebo are planned to be administered IV over 60 minutes (±15 minutes) by trained site personnel under the supervision of the investigator or their designee. Study treatment administration are recorded in the source documentation and in the electronic Case Report Form (eCRF), in particular planned infusion volume, actual infusion volume, and start and stop times of infusion, if the infusion was interrupted and if yes, reason for interruption.

Exposure to study drug will be listed for the Safety Analysis Set.

4.3. Protocol Deviations

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

- Failure to meet inclusion/exclusion criteria
- Failure to comply with Good Clinical Practice (GCP) guidelines will result in an important protocol deviation; Alector will determine if an important protocol deviation will result in withdrawal of a subject from the trial.

All important protocol deviations will be listed.

4.4. Adverse Events

AEs are collected regardless of cause or relationship that occur after signing of informed consent through end of study visit. Treatment emergent adverse events are those AEs with a start date on or after the date of first administration of investigational product. All AEs will be listed with a flag to indicate if an AE is treatment emergent.

In addition, all serious adverse events (SAEs) and AEs leading to discontinuation of study medication will be listed, with a flag to indicate if an AE is treatment emergent.

4.5. Laboratory Assessments and Laboratory Abnormalities

Laboratory assessments include: hematology, chemistry, urinalysis, and coagulation. On dosing days, in the event of an infusion-related reaction (IRR), blood will also be drawn for PK serum and ADA assessments, and blood will also be drawn at 1 to 2 hours and 48-72 hours after the IRR to assess C-reactive protein (CRP), ferritin, tryptase, and IL-6 levels.

Laboratory assessments will be listed. Any values that are outside of normal ranges will be flagged in the listings.

All laboratory assessments collected in the case of an IRR will be listed separately.

4.6. Vital Signs and 12-lead ECGs

All vital signs and 12-lead ECG data will be listed.

4.7. ALSFRS-R

ALSFRS-R total scores and changes from baseline will be listed.

Document Approvals

Approval Task Verdict: Approve	Brian Mangal, ([redacted]) Author Approval 30-Nov-2022 17:25:55 GMT+0000

Approval Task Verdict: Approve	Lawrence Carter, ([redacted]) Management Approval 30-Nov-2022 18:08:33 GMT+0000