CLINICAL STUDY PROTOCOL

Protocol Title	A Phase IIa Trial to Evaluate the Safety, Tolerability, and Biological Activity of LAM-002A (apilimod dimesylate capsules) in C9ORF72-Associated Amyotrophic Lateral Sclerosis
Study Sponsor	AI Therapeutics, Inc. 530 Old Whitfield St Guilford CT, 06437
Investigational Product	LAM-002A
Protocol Number	LAM-002A-ALS-CLN01
Developmental Phase	Phase IIa
US IND Number	147731
Protocol Versions (Date)	Version 7 (5 January 2023)

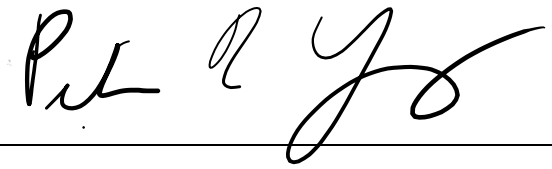
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AI THERAPEUTICS, INC. APPROVAL PAGE

Title	A Phase IIa Trial to Evaluate the Safety, Tolerability, and Biological Activity of LAM-002A (apilimod dimesylate capsules) in C9ORF72-Associated Amyotrophic Lateral Sclerosis.
Protocol Number	LAM-002A-ALS-CLN01
Version (Date)	Version 7 (5 January 2023)

By signing this document, it is confirmed on behalf of AI Therapeutics, Inc., that this study will be conducted and reported in compliance with the protocol, accepted standards of Good Clinical Practice (GCP), and all applicable regulatory requirements.



5 January 2023

Peter R. Young, Ph.D.
Chief Scientific Officer
AI Therapeutics, Inc.

Date

PRINCIPAL INVESTIGATOR APPROVAL PAGE

Title	A Phase IIa Trial to Evaluate the Safety, Tolerability, and Biological Activity of LAM-002A (apilimod dimesylate capsules) in C9ORF72-Associated Amyotrophic Lateral Sclerosis (ALS).
Protocol Number	LAM-002A-ALS-CLN01
Version (Date)	Version 7 (5 January 2023)

I have reviewed the protocol. On behalf of my institution, I agree to conduct the study as outlined in the study protocol and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements.

Principal Investigator Signature **Date**

Principal Investigator Printed Name

Institution:

Address:

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	Alzheimer's disease
AE	Adverse event
ALT	Alanine aminotransferase
ALS	Amyotrophic Lateral Sclerosis
ALS-CBS	ALS-Cognitive Behavioral Scale
ALSFRS-R	ALS Functional Rating Scale-Revised
AS	As-Treated
AST	Aspartate aminotransferase
AUC_{0-t}	Area under the plasma concentration *versus* time curve, as determined by a trapezoidal method, from time zero to t hours post-dose
AUC_{0-24}	Area under the curve 0-24 hours
βHCG	Beta human chorionic gonadotropin
BID	Twice per day
BUN	Blood urea nitrogen
CBC	Complete Blood Count
C-CASA	Columbia Classification Algorithm for Suicide Assessment
CFR	Code of Federal Regulations
CK	Creatine kinase
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximal plasma concentration
cm	Centimeter
CNS	Central Nervous System
CRF	Case Report Form
CRO	Contract research organization
CSF	Cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	Cytochrome P450 3A4 or CYP2C9
C9ALS	C9ORF72-associated ALS
DLTs	Dose-limiting toxicities
DNA	Deoxyribonucleic acid
DPRs	Dipeptide repeat proteins
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCLCR	Estimated creatinine clearance
eCRF	Electronic Case Report Form
EDC	Electronic data system
ELISA	Enzyme-linked immunosorbent assay
ET	Early termination
FDA	Food and Drug Administration

Abbreviation	Definition
FDAMA	Food and Drug Modernization Act of 1997
FSH	Follicle-stimulating hormone
FTD	Frontotemporal dementia
FVC	Forced vital capacity
GCP	Good clinical practice
HDPE	High density polyethylene
HTE	Heterogeneity of treatment effect
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
iMN	Patient derived motor neurons
in	Inches
IND	Investigational New Drug
INR	International normalized ratio
iPSC	Induced pluripotent stem cells
IRB	Institutional Review Board
kg	Kilogram
lbs	Pounds
LDH	Lactate dehydrogenase
LP	Lumbar puncture
MOP	Manual of procedures
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical Monitor
mg	Milligram
n	Number of Observations
NEALS	Northeast ALS Consortium
NfL	Neurofilament light chain
NHL	Non-Hodgkin Lymphoma
NSAID	Nonsteroidal anti-inflammatory drugs
OLE	Open-label extension
PBMC	Peripheral blood mononuclear cells
PD	Parkinson’s Disease
PI	Phosphatidylinositol
PI3P	Phosphatidylinositol 3-phosphate
PIKfyve	Phosphatidylinositol-3-phosphate- 5 kinase
PK	Pharmacokinetics
pNfH	phosphorylated neurofilament heavy chain
PO	Per os (by mouth)
PP	Per protocol
PT	Prothrombin time

Abbreviation	Definition
PTT	Partial thromboplastin time
QD	Once a day
QT	Time of start of Q wave until end of T wave in the heart's electrical cycle
RAN	Repeat-associated non-AUG
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
sGPNMB	Soluble GPNMB
SI	Site Investigator
SoA	Schedule of activities
SOC	System organ class
ST	Safety and Tolerability
SUSAR	Suspected unexpected serious adverse reactions
SVC	Slow vital capacity
TEAE	Treatment Emergent Adverse Event
TFEB	Transcription Factor EB
TLR	Toll-like receptor
T_{max}	Time to maximum concentration
VC	Vital capacity
WBC	White blood cell

1. PROTOCOL SYNOPSIS AND SCHEDULE OF ACTIVITIES

Study Title	A Phase IIa Trial to Evaluate the Safety, Tolerability, and Biological Activity of LAM-002A (apilimod dimesylate capsules) in C9ORF72-Associated Amyotrophic Lateral Sclerosis.
Study Number	LAM-002A-ALS-CLN01
Investigational Medicinal Product	LAM-002A (Apilimod dimesylate capsules)
Clinical Phase	Phase IIa
Sponsor	AI Therapeutics, Inc. 530 Old Whitfield Street Guilford, Connecticut 06437

Study Objective(s)

Primary Objective(s):

- To evaluate the safety of LAM-002A administration in C9ORF72-associated ALS (C9ALS)
- To evaluate the tolerability of LAM-002A administration in C9ALS
- To characterize LAM-002 and its active metabolites in the plasma and cerebrospinal fluid (CSF).

Secondary Objective(s):

- To evaluate the LAM-002A-induced biomarker sGPNMB in the plasma and CSF

Exploratory Objective(s):

- To evaluate the biological activity of LAM-002A as measured by exploratory markers of neurodegeneration, gene expression, and target engagement in CSF, PBMCs, and plasma including but not limited to:
  - CSF and PBMC levels of poly (GP) dipeptide repeat proteins (DPRs).
  - Plasma and CSF levels of neurofilament light chain (NfL).
- To evaluate the impact of LAM-002A on clinical measures of disease progression.

Study Design:

Study Parts A and B

This is a Phase 2a, multicenter, randomized, double-blind, placebo-controlled, biomarker-driven clinical trial evaluating the safety, tolerability, and biological effect of LAM-002A in approximately 12 adults with C9ORF72-associated ALS (C9ALS).

In Part A of the study, approximately twelve C9ALS participants will receive either standard of care plus LAM-002A or standard of care and placebo (randomized 2:1) for the first 12 weeks of the study (Core Study). LAM-002A will be administered as oral capsules 125 mg

BID (250 mg total daily dose). The LAM-002A dose may be reduced to 100 mg BID (200 mg total daily dose) if expected gastrointestinal side effects develop.

Participants who complete the first 12 weeks of the Core Study will be eligible to receive active drug (LAM-002A capsules at maximum tolerated dose of 125 or 100 mg BID) for the remainder of the study (open-label extension [OLE]) up to Week 24.

In Part B of the study, participants who complete Part A Week 24 on study drug, will be offered the opportunity to opt-in to continue the open-label extension for an additional 36 weeks starting at the Week 24 visit. Participants who elect not to roll over into Part B will complete the Day 168 visit, followed by a final safety telephone call visit at Week 28 to complete study participation. Participants who opt-in to Part B for an additional 36 weeks will have their end of study safety telephone call at Week 64.

Refer to the Schedule of Activities for the assessments to be performed at each study visit in Parts A and B of the study.

Study Part C

Part C of the study has been added to provide the opportunity for study participants who have tolerated open-label LAM-002A therapy in Part A or B of the study to continue open-label LAM-002A if they do not wish to transfer to the recently FDA-approved therapy for ALS, sodium phenylbutyrate/taurursodiol (Relyvrio™). Given the potential for drug-drug interactions, concurrent administration of LAM-002A and sodium phenylbutyrate/taurursodiol will not be permitted in this study.

Part C will be available to study participants at each study center upon activation of Version 7 of the protocol at that center. Study participants who decide not to or are unable to initiate standard-of-care sodium phenylbutyrate/taurursodiol therapy and wish to continue LAM-002A beyond their final Part B visit, may be considered for extended access to LAM-002A in Part C of the protocol. Such participants must not initiate sodium phenylbutyrate/taurursodiol or enroll in any other ALS investigational drug trial while concomitantly taking LAM-002A. Such participants must continue to receive ALS clinical care and safety laboratory monitoring consistent with conventional practice standards as deemed appropriate by the treating investigator and/or in collaboration with their clinical treating physicians. Before initiating any new medications, including non-prescription compounds or non-drug therapies, participants should consult with the treating investigator or qualified designee to evaluate for any potential safety risks. The treating health care provider should discuss with the sponsor any significant concerns that arise relating to individual participants to determine if it is appropriate for the participant to continue treatment with LAM-002A.

LAM-002A will be dispensed to Part C study participants per procedures acceptable to each site; sufficient LAM-002A will be dispensed by site personnel at intervals of approximately 12 weeks during in-person standard-of-care ALS clinic visits or shipped to participants per each site's standard practices. Therapy in Part C may continue in the absence of sodium phenylbutyrate/taurursodiol initiation, another protocol-defined reason for discontinuing LAM-002A, or study termination as defined in the Section 8.5 of the study protocol. During Part C, adverse events (AEs), and the use of concomitant therapies or procedures will be recorded in source documents or participant's medical records per standard-of-care

practices at each site. The sites must report any serious adverse events (SAEs) to the study sponsor per the procedures established in Section 9.8.1 of the protocol.

Study drug accountability and disposition will be managed per site procedures consistent with Section 13.11 of the protocol; relevant pharmacy records may be collected by the sponsor to document study drug disposition.

The study (including Part C of the trial) may be terminated at any time by the site investigator or the sponsor for valid medical or administrative reasons per Section 13.19 of the protocol.

Product Description:

LAM-002A (apilimod dimesylate) is a first-in-class inhibitor of phosphatidylinositol-3-phosphate 5-kinase (PIKfyve). PIKfyve is an endosomal lipid kinase that regulates endosomal membrane trafficking and lysosomal homeostasis. Pharmacological inhibition of PIKfyve with LAM-002A activates TFEB, a transcription factor that drives lysosomal biogenesis and clearance of toxic aggregates.

Each Size 0 capsule of the active drug contains 25 mg of LAM-002A (equivalent to 17.1 mg of apilimod free base). Inactive components in the capsules are microcrystalline cellulose, silicified microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.

Each Size 0 capsule of the placebo is identical in appearance to capsules containing the active drug. Each placebo capsule contains microcrystalline cellulose as the inactive ingredient.

All inactive excipients are within the limits of FDA's Inactive Ingredient (IIG) limit requirements.

Study Activities:

The specific study procedures and timing of activities to be conducted for each subject enrolled in the study are presented in tabular form in Table 1. Physical examinations, other clinical evaluations, and additional laboratory studies or more frequent assessments may be performed consistent with appropriate medical care for the subject, but these data will not necessarily be collected unless specified in Table 1.

Missed or delayed procedures or evaluations should be performed as close to the originally scheduled date/time as possible. Based on the medical monitor's judgment, an exception can be made when rescheduling becomes medically unnecessary because it is too close in time to the next scheduled procedure or evaluation. In that case, the missed evaluation may be omitted after consultation with the medical monitor.

Table 1. Schedule of Activities

Study Period	Pre-Treatment	Treatment Period Part A					Treatment Period Part B[10]						Post-treatment Follow Up[14]
		Placebo-Controlled Core Study			Open-Label Extension		Open-Label Extension						
Visit Name	Screening Visit	Baseline Visit	Week 2 Visit	Week 4, 8, 12 Visits	Week 16, 20 Visits	Week 24 Final Study Visit / Early Termination Visit	Week 28 Telephone call	Week 36 Visit	Week 42 Telephone call	Week 48 Visit	Week 54 Telephone call	Week 60 Final Treatment Visit[13]	Week 28 or 64 Telephone call end of study
Visit Timing (Visit Window)	1-21 days from Baseline Visit	Day 0	Day 14 (± 4d)	Days 28, 56, 84 (± 4d)	Days 112, 140 (± 4d)	Day 168 (± 4d)	Day 196 (±4d)	Day 252 (±4d)	Day 294 (±4d)	Day 336 (±4d)	Day 378 (±4d)	Day 420 (±4d)	Day 448 (±4d)
Written informed consent	X					X[11]							
Eligibility review	X												
Medical and ALS history	X												
Demographics	X												
El Escorial criteria	X					X						X	
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (blood pressure, pulse, respiration, and body temperature)	X	X	X	X	X	X		X		X		X	
Weight	X	X	X	X	X	X		X		X		X	
Height	X												
Physical examination	X			X[1]		X		X		X		X	
Neurological examination	X			X[1]		X		X		X		X	
12-lead ECG[2]	X												

Study Period	**Pre-Treatment**	**Treatment Period Part A**					**Treatment Period Part B[10]**						**Post-treatment Follow Up[14]**
		Placebo-Controlled Core Study			**Open-Label Extension**		**Open-Label Extension**						
Visit Name	**Screening Visit**	**Baseline Visit**	**Week 2 Visit**	**Week 4, 8, 12 Visits**	**Week 16, 20 Visits**	**Week 24 Final Study Visit / Early Termination Visit**	**Week 28 Telephone call**	**Week 36 Visit**	**Week 42 Telephone call**	**Week 48 Visit**	**Week 54 Telephone call**	**Week 60 Final Treatment Visit[13]**	**Week 28 or 64 Telephone call end of study**
Visit Timing (Visit Window)	**1-21 days from Baseline Visit**	**Day 0**	**Day 14 (± 4d)**	**Days 28, 56, 84 (± 4d)**	**Days 112, 140 (± 4d)**	**Day 168 (± 4d)**	**Day 196 (±4d)**	**Day 252 (±4d)**	**Day 294 (±4d)**	**Day 336 (±4d)**	**Day 378 (±4d)**	**Day 420 (±4d)**	**Day 448 (±4d)**
Screening laboratory sample collection for eligibility[3]	X												
Safety laboratory sample collection[4]		X		X	X	X		X		X		X	
Blood Biomarker sample collection[5]		X	X	X	X	X							
Plasma PK sample collection for LAM-002/ metabolites exposure[5]		X	X	X	X	X							
CSF sample collection for biomarkers and LAM-002/ metabolites exposure[6]		X		X		X							
ALSFRS-R		X		X	X	X	X	X		X		X	X
ALS-CBS		X		X[7]		X							
Vital capacity (VC)	X	X		X	X	X		X		X		X	
Baseline C-SSRS	X												
"Since Last Visit" C-SSRS		X	X	X	X	X		X		X		X	

Study Period	Pre-Treatment	Treatment Period Part A					Treatment Period Part B[10]						Post-treatment Follow Up[14]
		Placebo-Controlled Core Study			Open-Label Extension		Open-Label Extension						
Visit Name	**Screening Visit**	**Baseline Visit**	**Week 2 Visit**	**Week 4, 8, 12 Visits**	**Week 16, 20 Visits**	**Week 24 Final Study Visit / Early Termination Visit**	**Week 28 Telephone call**	**Week 36 Visit**	**Week 42 Telephone call**	**Week 48 Visit**	**Week 54 Telephone call**	**Week 60 Final Treatment Visit[13]**	**Week 28 or 64 Telephone call end of study**
Visit Timing (Visit Window)	**1-21 days from Baseline Visit**	**Day 0**	**Day 14 (± 4d)**	**Days 28, 56, 84 (± 4d)**	**Days 112, 140 (± 4d)**	**Day 168 (± 4d)**	**Day 196 (±4d)**	**Day 252 (±4d)**	**Day 294 (±4d)**	**Day 336 (±4d)**	**Day 378 (±4d)**	**Day 420 (±4d)**	**Day 448 (±4d)**
Adverse event review		X	X	X	X	X	X	X	X	X	X	X	X
Subject Dosing Diary Dispensing & Review		X	X	X	X	X		X		X		X	
Dispensing of Study Drug		X	X	X	X	X[12]		X		X			
Perform study drug compliance and accountability			X	X	X	X	X	X		X		X	
Administration of LAM-002A drug in clinic[8]		X	X	X	X	X[9]							

1. Physical and Neurological Exam to be performed at Screening Visit and follow-up visits Week 12, and 24/ET.
2. 12-lead ECG to be performed at Screening Visit. If clinically significant ECG abnormalities are present, ECG will be repeated prior to Baseline Visit and during the study, at the SI and medical monitor's discretion.
3. HIV, Hepatitis B, and Hepatitis C, CBC with differential, full chemistry panel, liver function tests, and INR/PT/PTT will be assessed by a central lab. A urinalysis and urine pregnancy test (in women of childbearing age only) will be performed locally. Screening labs will also include collection of a DNA sample for genotyping and repeat testing for the C9orf72 expansion at a central lab as needed, which may be performed at screening if indicated for eligibility.
4. CBC with differential, full chemistry panel, liver function tests, INR/PT/PTT to be assessed by a central laboratory. A urinalysis and urine pregnancy test (in women of childbearing potential only) will be performed locally.
5. Blood biomarker collection for plasma and PBMC will be obtained prior to dosing at the baseline visit and 1h ± 30 minutes after dosing for the follow-up visits. Time of last dose and sample collection time will be recorded.
6. For all participants, CSF samples will be obtained at the Baseline Visit and follow-up visits Week 4, 8, 12 and 24/ET. Approximately 10-15 mL of CSF will be collected: prior to dosing at the Baseline visit, and 1h ± 30 minutes after dosing for the follow-up visits Week 4, 8, 12, and 24/ET. Time of last dose and CSF collection time will be recorded.
7. ALS-CBS to be performed at follow-up visits Week 8, 12, and 24/ET.

8. At all Part A study visits beyond the Screening Visit, study participants should ingest the study drug (LAM-002A) while fasting (defined as no food with the exception of clear liquids for ≥4 hours before and ≥2 hour after dosing) and in the presence of study staff to ensure correct timing of pre-dosing plasma collection and post-dosing CSF and plasma collection. Study drug taken on non-study visit days can be taken in the non-fasting state.
9. Subjects who have discontinued study drug prior to the Week 24 visit will not receive a dose in clinic at their Early Termination Visit.
10. Additional opt-in open label extension for Part A Week 24/Day 168 completers
11. Patients choosing to participate in Part B should be reconsented for this portion of the study
12. For subjects choosing not to participate in Part B, no drug should be dispensed.
13. Final treatment visit for subjects in Part B including early terminators for both Part A and Part B
14. Subjects opting to not participate in Part B on week 24 (day 168) and subjects completing treatment to week 60 or terminating treatment during any part of the study (Parts A and B) should have an end of study follow up telephone visit

2. INTRODUCTION

2.1. Study Rationale

ALS is a progressive neurodegenerative disease of the motor neurons of the brain and spinal cord, leading to muscle weakness, paralysis and ultimately death from respiratory failure within 2 to 5 years of diagnosis in most patients (Brooks 1996). Causes can be both familial and sporadic. In 2014, 15,927 patients were identified as having ALS in the United States. There are only 2 approved drugs, riluzole and edaravone, that have very limited efficacy and confer only a modest survival benefit in all forms of ALS (Miller 2012; Writing Group 2017).

Recent understanding of the molecular drivers of ALS has been enhanced by the discovery of familial and spontaneous mutations. In 2011, the hexanucleotide intronic repeat expansion (GGGGCC) in the *C9ORF72* gene was first described as the most common cause of familial ALS (DeJesus-Hernandez 2011; Renton 2011; Gijselinck 2012). This 100-1000-fold repeat of G4C2 in the first intron of the gene *C9ORF72*, accounts for up to 50% of familial ALS and up to 10% of sporadic ALS (Majounie 2012; Zou 2017). In C9ORF72 ALS, the median age of onset is 57.9 ($\pm$ 8.3) years with an average survival of 36.9 months after onset (Cammack 2019). ALS patients harboring the *C9ORF72* repeat expansion also have an increased predilection for bulbar-onset and a coincidence of frontotemporal dysfunction (Ghasemi 2018).

The use of novel ALS model systems including patient derived motor neurons (iMN) (differentiated from induced pluripotent stem cells (iPSC)), and transgenic animal models have contributed to a better mechanistic understanding of C9ORF72 ALS. The *C9ORF72* repeat expansion induces the accumulation of dipeptide repeat proteins (DPRs) (generated from repeat-associated non-AUG (RAN) translation) and also causes sequestration of RNA binding proteins which both contribute to neurotoxicity (Brown 2017). The C9ORF72 protein is also a key negative feedback regulator of the autophagy-lysosome pathway (Amick 2017; Zhang 2018; Liu 2019). Accordingly, experiments suggest that reduced C9ORF72 expression due to the repeat expansion causes lysosomal deficiency and impaired clearance driving the accumulation of glutamate receptors and neurotoxic dipeptide repeat proteins (Shi 2018; Staats 2019). Thus, the *C9ORF72* repeat expansion both induces the expression of neurotoxic protein and RNA species and increases sensitivity to excitotoxic stimuli.

2.2. Background

2.2.1. LAM-002A Mechanism of Action

Based on its original discovery as an inhibitor of the common p40 subunit of IL-12 and IL-23 and before the molecular target was known, a previous sponsor, Synta Pharmaceuticals, pursued clinical development of apilimod dimesylate (LAM-002A) in inflammatory indications under IND 70204 and IND 62112. Subsequently AI Therapeutics, Inc. acquired commercial rights to apilimod dimesylate/apilimod from Synta and opened IND 125763 on 2 October 2015 to pursue clinical development in non-Hodgkin lymphoma (NHL). Under these INDs over 800 subjects have been exposed to doses of LAM-002A up to 150 mg and 210 mg (free base) for periods of over a year. Summaries of the LAM-002A and apilimod nonclinical pharmacology program are provided in IND 125763, Module 2.6.2.

LAM-002A (apilimod dimesylate capsule) is a first-in-class inhibitor of phosphatidylinositol-3-phosphate 5-kinase (PIKfyve) with an IC_{50} of 14nM and K_d of approximately 75 pM (range 69-81 pM) (Gayle 2017; Cai 2013). PIKfyve, is a 240-kDa endosomal phosphatidylinositol (PI) 5 lipid kinase that catalyzes the phosphorylation of phosphatidylinositol 3-phosphate (PI(3)P) to phosphatidylinositol 3,5-bisphosphate ($PI(3,5)P_2$). PIKfyve normally synthesizes PI(3,5)P2 on endosomes and lysosomes, supporting lysosomal homeostasis (Rutherford 2006). Pharmacological inhibition of PIKfyve with apilimod increases the activity of transcription factor EB (TFEB) (Gayle 2017), a master gene for lysosomal biogenesis that coordinates expression of lysosomal hydrolases, membrane proteins and genes involved in autophagy (Settembre 2011). Active, nuclear TFEB levels have been found to be decreased in the brains of patients with ALS and AD (Wang 2016). Furthermore, published work has shown that activating TFEB through viral overexpression in neurodegenerative models of Parkinson's disease (PD) and Alzheimer's disease (AD) can clear protein aggregates, protect neurons, and ameliorate behavioral phenotypes (Decressac 2013, Polito 2014; Xiao 2014). Together these data support the hypothesis that LAM-002, through activation of TFEB, can clear pathogenic protein aggregates and protect neurons.

Like other neurodegenerative diseases, amyotrophic lateral sclerosis (ALS) is characterized by autophagy and lysosomal disfunction and pathogenic protein aggregate formation (Bertram 2005). Primary pharmacodynamics data in patient-derived induced motor neurons (iMN) and mouse models of ALS show that *C9ORF72* mutation confers lysosomal deficiency and associated vulnerability to degenerative stimuli in neurons, including neurotrophic growth factor withdrawal, glutamate-induced excitotoxicity, and DPR aggregates. Consistent with its ability to activate TFEB, apilimod treatment ameliorated these deficits, improving neuron survival and reversing the accumulation of DPR aggregates (Shi 2018; Staats 2019). Furthermore, neuroinflammation is known to be an early signal and driver of progression in many neurodegenerative diseases (Geloso 2017; Bertram 2005). Similar to its effects on PBMCs (Wada 2007), apilimod also potently inhibits the activation of microglial cells in vitro as demonstrated by the inhibition of the release of IL-12/IL-23 p40 production in response to toll-like receptor (TLR) activation. Coupled to its ability to inhibit inflammatory cytokine induction, apilimod therefore holds promise as a therapeutic for ALS.

2.2.2. Human Experience with LAM-002A

LAM-002A (apilimod dimesylate) or the apilimod free base has undergone extensive clinical investigation. In the clinical trials program, >800 study subjects have received apilimod dimesylate or apilimod, including healthy subjects participating in pharmacology studies, patients with nonmalignant inflammatory conditions and patients with B-cell hematological cancers.

2.2.2.1. Safety and Tolerability

LAM-002A has a well-established clinical record supporting its safety and tolerability, including published literature (LAM-002A IB V5). Under IND 125,763, AI Therapeutics sponsored a Phase 1 dose-ranging and expansion study evaluating the safety, pharmacokinetics, pharmacodynamics, and anticancer activity of LAM-002A in subjects with recurrent, previously treated non-Hodgkin lymphoma (NHL). Study results indicate that LAM-002A is very well tolerated and has a favorable safety profile at doses of ≤ 125 mg BID (250 mg total daily dose).

Most observed adverse events or laboratory abnormalities have been low-grade, infrequent, and largely attributable to the underlying disease, prior therapy, concomitant medications, or other conditions. Continuous oral administration of LAM-002A has been well tolerated in humans with dosing regimens of ≤125 mg BID (≤250 mg total daily dose). In subjects with cancer, dosing regimens of 150 mg BID (300 mg QD) or 75 mg TID (225 mg QD) were not well tolerated due to symptoms of nausea, vomiting, and diarrhea that effectively precluded drug compliance in most subjects. However, when administered at 125 mg BID, the drug demonstrated anticancer efficacy, and was well tolerated with excellent compliance, over a year (Diefenbach, 2020). Toxicities at this dose level were infrequent nausea, vomiting, and/or diarrhea, requiring dose reduction to 100 mg BID in <10% of subjects. Accordingly, this same dosing regimen is proposed for evaluation in this study in study participants with C9ORF72 ALS.

2.2.2.2. LAM-002A Pharmacokinetics in Humans

The pharmacokinetics of LAM-002A was studied in healthy subjects and in subjects with hematological cancers as a monotherapy and in combination with rituximab, or atezolizumab. LAM-002 (apilimod free base of LAM-002A) was rapidly bioavailable following oral dosing with an approximate T_{max} of 1 hour. The C_{max} and AUC_{0-8} generally increased with increasing dose; the Day 8 AUC_{0-8} showed the closest relationship to dose proportionality. As steady-state exposures were achieved, mean Day 8/Day 1 accumulation indices (AI) for C_{max} and AUC_{0-8} across all dose levels were 1.3 and 1.7, respectively. Mean terminal $t_{1/2}$ values ranged from 2.7 to 3.9 hours on Day 1 and from 5.4 to 7.0 hours on Day 8 and did not show dose dependency. On the first day of administration, ~90% of the drug was cleared within 10 hours after which the remaining drug was eliminated with a terminal $t_{1/2}$ of 5 to 10 hours. The terminal $t_{½}$ increased to 12 to 21 hours on Day 14 in healthy subjects.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of LAM-002A may be found in the LAM-002A IB V5.

There have been no subjects with C9ORF72 ALS evaluated to date, and the risk/benefit of LAM-002A in C9ORF72 ALS is not understood. The safety and tolerability of LAM-002A has been established, with >800 subjects treated with the drug as of March 20, 2020. Overall, product administrations were well tolerated. Gastrointestinal TEAEs of nausea, vomiting, and diarrhea were commonly observed, and showed dose dependency, with most TEAEs being of Grade 1 or 2. At 125 mg BID. LAM-002A was found to be safe and tolerable.

3. STUDY OBJECTIVES

3.1. Primary Objectives

- To evaluate the safety of LAM-002A administration in C9ORF72-associated ALS (C9ALS).
- To evaluate the tolerability of LAM-002A administration in C9ALS.
- To characterize LAM-002 and its active metabolites in the plasma and CSF.

3.2. Secondary Objectives

- To evaluate the LAM-002A-induced biomarker sGPNMB in the plasma and CSF.

3.3. Exploratory Objectives

- To evaluate the biological activity of LAM-002A as measured by exploratory markers of neurodegeneration, gene expression, and target engagement in CSF, PBMCs, and plasma including but not limited to:
    - CSF and PBMC levels of poly (GP) dipeptide repeat proteins (DPRs).
    - Plasma and CSF levels of neurofilament light chain (NfL).
- To evaluate the impact of LAM-002A on clinical measures of disease progression.

4. STUDY ENDPOINTS

4.1. Primary Endpoints

- Safety: Defined as the occurrence of serious and non-serious treatment-emergent adverse events (TEAEs) and clinically significant treatment-emergent abnormalities in clinical and laboratory values.
- Tolerability: Defined as the percentage of participants who complete 12 weeks on study treatment during the Core Study. Secondary measures of tolerability will consider completion of 12 weeks on open-label study treatment during the OLE.
- Changes in plasma and CSF levels of LAM-002 and its active metabolites from pre-treatment to near-peak samples (1h ± 30 minutes after dosing) while on treatment.

4.2. Secondary Endpoints

- Changes in plasma and CSF levels of the LAM-002A-induced biomarker sGPNMB.

4.3. Exploratory Endpoints

- Change in ALS Functional Rating Scale Revised (ALSFRS-R) total and domain scores.
- Change in vital capacity (VC)
- Permanent assisted ventilation-free survival*
- Change in ALS-Cognitive Behavioral Scale (ALS-CBS)
- Changes in biomarkers of neurodegeneration, gene expression, and target engagement in CSF, PBMCs, and plasma including but not limited to:
  - CSF and PBMC levels of poly (GP) dipeptide repeat proteins (DPRs).
  - Plasma and CSF levels of neurofilament light chain (NfL).

***** Assisted ventilation will be defined as permanent when non-invasive or invasive ventilation is used for >22 hours in a 24-hour period, for 7 consecutive days. Date started is the first day of the 7-day period.

5. STUDY DESIGN AND CONDUCT

5.1. Study Design

5.1.1. Study Parts A and B

This is a Phase 2a, multicenter, randomized, biomarker-driven clinical trial evaluating the safety, tolerability, and biological effect of LAM-002A in approximately 12 adults with C9ORF72-associated ALS and (C9ALS).

Informed consent will be obtained prior to the conduct of any study-related procedures. Study eligibility will be assessed at the screening visit and during the screening period. A baseline visit will occur within 3 weeks of screening.

In Part A of the study, approximately twelve C9ALS participants will receive either standard of care plus LAM-002A or standard of care and placebo (randomized 2:1) for the first 12 weeks of the study (Core Study). LAM-002A will be administered as oral capsules 125 mg BID (250 mg total daily dose). The LAM-002A dose may be reduced to 100 mg BID (200 mg total daily dose) if expected gastrointestinal side effects develop.

Participants who complete the first 12 weeks on treatment will be eligible to receive active drug (LAM-002A capsules at maximum tolerated dose of 125 or 100 mg BID) for the remainder of the study (OLE) up to Week 24. At this time, the study sponsor will conclude Part A of the study, will collate and verify all study data through an appropriate data cut-off date, and will perform an interim database lock for an analysis of the Part A per-protocol study data and preparation of a study report.

In Part B of the study, participants will be offered the opportunity to continue in an open label extension for up to 9 months starting at the Week 24 visit at the LAM-002A dose used in Part A. Data acquired from Part B will serve to provide preliminary data on the long-term safety and tolerability of LAM-002A in ALS and inform future studies in ALS.

Participants can withdraw from the study at any time. Subjects in Parts A and B who discontinue study therapy will complete an Early Termination visit as soon as possible. Discontinued subjects will also complete the Follow-Up Period of the study by completing the final Follow-up Telephone Call Visit, 4 weeks post their Early Termination Visit.

Refer to the Schedule of Activities (Table 1) for the assessments to be performed at each study visit

5.1.2. Study Part C

Part C of the study has been added to provide the opportunity for study participants who have tolerated open-label LAM-002A therapy in Part A or B of the study to continue open-label LAM-002A if they do not wish to transfer to the recently FDA-approved therapy for ALS, sodium phenylbutyrate/taurursodiol (Relyvrio™). Given the potential for drug-drug interactions, concurrent administration of LAM-002A and sodium phenylbutyrate/taurursodiol will not be permitted in this study.

Part C of the study will be available to study participants at each study center upon activation of Version 7 of the protocol at that center. Study participants who decide not to or are unable to

initiate standard-of-care sodium phenylbutyrate/taurursodiol therapy and wish to continue LAM-002A beyond their final Part B visit, may be considered for extended access to LAM-002A in Part C of the protocol. Such participants must not initiate sodium phenylbutyrate/taurursodiol or enroll in any other ALS investigational drug trial while concomitantly taking LAM-002A. Such participants must continue to receive ALS clinical care and safety laboratory monitoring consistent with conventional practice standards as deemed appropriate by the treating investigator and/or in collaboration with their clinical treating physicians. Before initiating any new medications, including non-prescription compounds or non-drug therapies, participants should consult with the treating investigator or qualified designee to evaluate for any potential safety risks. The treating health care provider should discuss with the sponsor any significant concerns that arise relating to individual participants to determine if it is appropriate for the participant to continue treatment with LAM-002A.

LAM-002A will be dispensed to Part C study participants per procedures acceptable to each site; sufficient LAM-002A will be dispensed by site personnel at intervals of approximately 12 weeks during in-person standard-of-care ALS clinic visits or shipped to participants per each site's standard practices. Therapy in Part C may continue in the absence of sodium phenylbutyrate/taurursodiol initiation, another protocol-defined reason for discontinuing LAM-002A, or study termination as defined in the Section 8.5 of the study protocol.

During Part C, AEs and the use of concomitant therapies or procedures will be recorded in source documents or participant's medical records per standard-of-care practices at each site. The sites must report any SAEs to the study sponsor per the procedures established in Section 9.8.1 of the protocol.

Study drug accountability and disposition will be managed per site procedures consistent with Section 13.11 of the protocol; relevant pharmacy records may be collected by the sponsor to document study drug disposition.

The study (including Part C of the trial) may be terminated at any time by the site investigator or the sponsor for valid medical or administrative reasons per Section 13.19 of the protocol.

5.2. Study Conduct

The study will be performed in accordance with the principles as set forth under the requirements of 21 Code of Federal Regulations (CFR) 50 and the ICH E6 GCP guideline. The research will be overseen by an institutional review board/independent ethics committee (IRB/IEC). The study protocol, any protocol amendments, informed consent documents, and any material used to describe the trial to potential subjects will be reviewed and approved by the IRB/IEC prior to the performance of any study-related procedures.

AI Therapeutics, Inc. will serve as the regulatory sponsor for the study and will maintain an investigational new drug (IND) application with the FDA. The protocol will be submitted to the IND for LAM-002A (IND#147731) and the trial design and results will be subject to review by the FDA.

The study will employ an independent Data Safety Monitoring Board (DSMB) for safety and clinical efficacy. Blinded and unblinded summary reports of all clinical Aes and SAEs and safety laboratory tests will be reviewed by the DSMB on an ongoing basis to identify any safety concerns. Conference calls among the members of the DSMB will be conducted periodically to

discuss study progress, exchange study information, and review safety events (in particular, DLTs; SAEs; adverse events of special interest; and Aes leading to dose interruption, dose reduction, or therapy discontinuation), and discuss potential amendments to the protocol.

The DSMB will be responsible for reviewing the interim safety and futility analyses and recommending study continuation, termination, or adaptation.

5.3. Rationale for Study Design

The control group will receive matching placebo capsules. A placebo group was chosen in order to determine whether the treatment (LAM-002A) demonstrates safety and tolerability and shows changes in biomarkers compared to the control.

This phase Iia study will lay the groundwork for a definitive phase II/III trial in several ways:

1. We will obtain broad safety and tolerability data up to 24 weeks
2. We will obtain evidence of CNS penetration of the study drug and biological activity on important pharmacodynamic biomarkers.

5.4. Justification for Dose

The dose of 125 mg BID LAM-002A (apilimod dimesylate) chosen for the trial in C9ORF72 ALS is based on safety, exposure, and efficacy data from a clinical trial in patients with B-cell lymphomas and from in vitro measurements of potency in preclinical studies.

The recommended dose of 125 mg BID was established in a Phase 1 population of 62 patients with previously treated, advanced, B-cell lymphomas. The study population median (range) of ages was 69 (46-89) years and patients were equally divided among males (n=32) and females (n=30). Patients typically had cancer-related symptoms and often had additional comorbidities (i.e., diabetes mellitus, chronic obstructive lung disease, cardiovascular disease). Thus, the population evaluated was highly relevant to the population being currently evaluated.

Among these 62 patients, 39 received the recommended LAM-002A oral, continuous dosing regimen of 125 mg BID, either alone or in combination with the anti-CD20 antibody, rituximab, or the anti-PD-L1 antibody, atezolizumab (neither of which had overlapping toxicities with LAM-002A). Durations of therapy extended to >600 days and therapy is still ongoing in several patients. Of importance, the ***only*** evident drug-related adverse events (Aes) observed with this LAM-002A dosing regimen were gastrointestinal in nature. When they occurred, such events were seen in a minority of patients, were typically low-grade, and were readily managed with dose modification. Over the entire course of chronic treatment lasting many months, incidences of Grade 1-4 gastrointestinal Aes of any cause were nausea in 14/39 (35.9%) patients, vomiting in 10/39 (25.6%) patients, and/or diarrhea in 10/39 (25.6%) patients. The incidences of Grade 3-4 gastrointestinal Aes of any cause were low: nausea in 2/39 (5.1%), vomiting in 1/39 (2.6%), and diarrhea in 0/39 (0%); in these patients, other reasons for such events were documented (i.e., central nervous system tumor, gastrointestinal lymphoma, or viral gastroenteritis). As a consequence of this excellent safety profile, median compliance with therapy was >97% in the 39 subjects. Symptoms leading to LAM-002A dose modification were primarily nausea or diarrhea and appeared to be LAM-002A-related in 4 (10.2%) subjects; gastrointestinal symptoms in these subjects lessened or resolve upon dose reduction and LAM-002A could be continued.

It should be further emphasized that LAM-002A did not cause any disabling or life-threatening toxicities.

Furthermore, clinical efficacy was observed in patients with follicular lymphoma at the recommended dose of 125 mg BID. Among the 17 patients with follicular lymphoma, 9 with follicular lymphoma were treated with LAM-002A monotherapy or LAM-002A-based combination therapy at this dose level and had substantial tumor regressions meeting established criteria for objective response (Diefenbach et al., 2020, Cheson 2014). Objective responses have been long-lasting, with durations exceeding 12 months among several subjects. When taken together with the safety and exposure data, these efficacy findings document that administration 125 mg BID of LAM-002A is pharmacologically active in producing a desired clinical effect with a well-tolerated dosing regimen.

LAM-002 (apilimod), the active form of LAM-002A, has potent nanomolar in vitro activity in activating TFEB and protecting motor neurons from glutamate toxicity. These active apilimod concentrations are similar to those active against B-cell non-Hodgkin lymphoma cell lines in vitro (Gayle 2017). Given the clinical responses observed in B-cell lymphoma patients at 125 mg BID and evidence of target inhibition in patient plasma samples, it would therefore be predicted that this dose would also provide efficacious drug levels in patients. Indeed, at 125 mg BID the plasma concentrations of active drug, which includes apilimod and its active metabolites (STA-5908, STA-5944, and STA-6048) weighted by their relative cell-based activity and exposure, exceed the in vitro active doses (50-100 nM) by 4 times at trough and by 20 times at Cmax. Furthermore, a rat distribution study of oral administration of LAM-002A suggests that apilimod brain exposure (AUC) is 3.1 times higher than in blood, providing further rationale that 125 mg BID would provide sufficient drug levels for activity in the central nervous system.

6. STUDY POPULATION

This clinical trial can fulfill its objectives only if appropriate participants are enrolled. The protocol-specified eligibility criteria are designed to select subjects for whom study participation is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a study candidate. Eligibility criteria may not be waived by the investigator and conformance to the eligibility criteria will be reviewed in the case of a GCP or a regulatory authority audit. Any questions regarding a study candidate's eligibility should be discussed with the medical monitor before enrollment.

6.1. Inclusion Criteria

Study candidates must meet all of the following inclusion criteria to be eligible for participation in this study:

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. If there is a strong clinical suspicion for C9ALS based on C9-positive family history and El Escorial Criteria consistent with a diagnosis of ALS, clinical testing for the C9ORF72 repeat expansion may be performed with study screening labs at the discretion of the SI, medical monitor, and study sponsor.

   AND

   b. Must meet possible, laboratory-supported probable, probable, or definite criteria for diagnosing 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 SI's opinion, and at the discretion of the medical monitor and study sponsor.
4. In the case that a participant lacks the ability to provide informed consent. Informed consent will be sought from the participant's surrogate representative.
5. Able to safely swallow study drug capsule at screening and throughout study. May use thickened substances to assist in swallowing drug.
6. Vital Capacity greater than and equal to 50% of predicted at the time of the Screening Visit measured by Slow Vital Capacity (SVC), or, if required due to COVID-19 pandemic-related restrictions and with Sponsor approval, Forced Vital Capacity (FVC) measured in-person or via telemedicine.
7. Participants must either not take or be on a stable dose of riluzole (as either a tablet or oral suspension) for > 30 days prior to the Screening Visit. Riluzole-naïve participants are permitted in the study.
8. Participants must either not take edaravone or have completed at least one 14-day cycle with plan for continuation of 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 visit. Edaravone-naïve participants are permitted in the study.

9. Participants must be able to complete all study procedures, including the lumbar punctures at the time of the Screening Visit, in the SI's opinion.
10. Geographically accessible to the site.

6.2. Exclusion Criteria

Study candidates who meet any of the following criteria will not be eligible for participation in this study:

1. Clinically significant unstable medical condition (other than ALS) that would pose a risk to the participant, according to the SI's judgment (e.g., cardiovascular instability, systemic infection, or clinically significant laboratory abnormality or ECG changes).
    a. Gastrointestinal disease (e.g., gastric, or intestinal bypass surgery, jejunostomy tube, pancreatic enzyme insufficiency, malabsorption syndrome, symptomatic inflammatory bowel disease, chronic diarrheal illness, bowel obstruction) that might interfere with drug absorption or with interpretation of gastrointestinal Aes. Gastrostomy tube placement is allowed prophylactically or to supplement nutrition/hydration but may not be used for study drug administration.
    b. Hepatic profile showing any of the following:
        i. Serum alanine aminotransferase (ALT) >5 × upper limit of normal (ULN).
        ii. Serum aspartate aminotransferase (AST) >5 × ULN.
        iii. Serum bilirubin >1.5 × ULN.
    c. Renal profile showing an estimated creatinine clearance (eClCR) <30 mL/minute (with eClCR to be calculated by the method at the laboratory performing the serum creatinine test).
2. Presence of a neurodegenerative cognitive or motor syndrome (e.g., Alzheimer's disease, Parkinson's disease) not related to the C9ORF72 repeat expansion.
3. Presence of unstable psychiatric disease or substance abuse that would impair ability of the participant to provide informed consent, in the SI's opinion.
4. Active cancer or history of cancer, except for the following: basal cell carcinoma or successfully treated squamous cell carcinoma of the skin, cervical carcinoma in situ, prostatic carcinoma in situ, or other malignancies curatively treated and with no evidence of disease recurrence for at least 3 years. Active cancer includes cancers with current disease manifestations or therapy that could adversely affect subject safety and longevity, create the potential for drug-drug interactions, or compromise the interpretation of study results.
5. Prior solid organ transplantation.
6. Ongoing immunosuppressive therapy including systemic or enteric corticosteroids at screening or for the duration of the trial, at the discretion of the site investigator and medical monitor.
7. Use within 5 days prior to randomization or for the duration of the trial of a strong inhibitor or inducer of cytochrome P450 (CYP) 3A4 or expected requirement for chronic use of a strong inhibitor or inducer of CYP3A4 during study therapy (see Appendix 15.1 for a list of

drugs known to be strong inhibitors or inducers of CYP3A4), at the discretion of the site investigator and medical monitor.

8. Use within 5 days prior to randomization or for the duration of the trial of drug that is a moderate-to-strong substrate of CYP2C9 (including warfarin, tolbutamide, phenytoin, glimepiride) or expected requirement for chronic use of such drugs during study therapy, at the discretion of the site investigator and medical monitor.
9. Use of investigational treatments for ALS (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 *(Please refer to the current list of experimental therapies maintained by the Medical Monitor).*
10. Exposure at any time to any gene therapies under investigation for the treatment of ALS (off-label use or investigational).
11. If female, breastfeeding, known to be pregnant, planning to become pregnant during the study, or of child-bearing potential and unwilling to use effective contraception for the duration of the trial and for 3 months after discontinuing treatment.
12. If male of reproductive capacity, unwilling to use effective contraception for the duration of the trial and for 3 months after discontinuing study treatment.
13. Anything that would place the participant at increased risk or preclude the participant's full compliance with or completion of the study, in the SI's opinion.
14. If a participant is being re-screened, the disqualifying condition has not been resolved, or the mandatory wash-out duration has not occurred.
15. Contraindication to undergoing a lumbar puncture (LP) in the SI's opinion. Participants undergoing the LP must not be currently taking anticoagulation and antiplatelet medications such as warfarin and clopidogrel bisulfate (Plavix™), that would be a contraindication to LP; aspirin and non-steroidal anti-inflammatories are allowed.

7. STUDY DRUG ALLOCATION

7.1. Randomization and Stratification

After a subject has completed the necessary screening assessments and has been confirmed to be eligible, the subject can be randomized into the study.

Participants will be randomized by permuted blocks in a single stratum at a 2:1 ratio (Arm A:Arm B) to either of the following treatment assignments:

- Arm A: LAM-002A
- Arm B: Matching placebo

7.2. Blinding

The identity of the treatments will be concealed by central blinding of study drug assignments. Blinding will be accomplished through use of a placebo that is well-matched to the active drug in appearance, packaging, labeling, and schedule of administration. During the study, subjects, caregivers, investigational site personnel, study sponsor study team members, and all other study personnel will remain blinded to the identity of the treatment assignments; these assignments will be available only to the unblinded randomization team, and the DSMB for the study, an independent bioanalytical group, and drug safety personnel who are not part of the study team. Unblinding during the study will only occur in the case of subject emergencies or as requested by the DSMB. Where required by local regulation, expedited reporting of serious adverse events to specific regulatory authorities will include information regarding the study drug treatment assignment (LAM-002A or placebo); this will be done in such a way that subjects, investigational site personnel, institutional review board/independent ethics committees (IRB/IEC), and study team members remain blinded as to the treatment assignment for the subject described in the adverse event report.

The final unblinded analysis of the study will only be performed when the database is completed and locked. While bioanalytical assays to determine LAM-002A concentrations may be performed prior to unblinding, pharmacokinetic data that would allow identification of treatment assignments for individual subjects will not be available to the study team until after the blind is broken and the primary analysis has occurred. Except for emergency unblinding, individual subjects, caregivers, and site personnel will not be informed of the randomized treatment assignments until the implications of revealing such data for the overall LAM-002A study program have been determined by the project leader for the LAM-002A development program.

7.3. Emergency Unblinding

Every attempt should be made to preserve the integrity of study drug (LAM-002A/placebo) blinding. Unblinding in individual subjects who experience adverse events is rarely required to provide effective intervention and support. For subjects having adverse events or laboratory abnormalities that require drug cessation or medical intervention, the investigational staff should strive to provide necessary support to the subject without breaking the blind. In the exceptional circumstances that knowledge of the study drug assignment appears essential for providing appropriate medical management, the investigator should contact the medical monitor to discuss

the rationale for breaking the blind and the adverse consequences of the unblinding for the subject's continued participation in the study. If the investigator still believes that unblinding is warranted, the investigator will be able to access the randomization system in order to obtain the treatment assignment for that subject. No randomization lists or other unblinding information will be provided to the site. After breaking the blind, the investigational site staff should record details regarding the reasons for breaking the blind and any adverse events leading to the breaking of the blind in the source documents and in the appropriate eCRF.

If the site breaks the blind, that subject will be discontinued from study therapy (LAM-002A or placebo).

8. STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT

8.1. Study Drug (LAM-002A and Placebo)

8.1.1. Description

LAM-002A is formulated in capsules containing 25 mg of apilimod dimesylate (equivalent to 17.1 mg of apilimod free base, respectively). The capsule is Swedish orange, Size 0 and has a total fill weight of 175 mg. Inactive components in active capsules are microcrystalline cellulose, silicified microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.

Placebo is identical in appearance to capsules containing the active drug. Each placebo capsules contains microcrystalline cellulose as the inactive ingredient.

All inactive excipients are within the limits of FDA's Inactive Ingredient (IIG) limit requirements.

8.1.2. Source

Study drug (LAM-002A) and matching placebo will be provided by the study sponsor.

8.1.3. Packaging and Labeling

Study drug (LAM-002A and placebo) is supplied in high-density polyethylene (HDPE) bottles, induction sealed with child resistant closures. Each bottle contains 100 capsules.

Labels for LAM-002A and placebo bottles meet all applicable FDA requirements.

Concurrent stability studies are ongoing for lots used in current clinical trials. Additionally, there is ICH stability data supporting 36 months of stability for drug product.

8.1.4. Shipping, Storage, and Stability

The LAM-002A and placebo capsules must be stored in a secure storage area, with limited access, at 2° C to 8°C.

8.1.5. Dispensing

A pharmacist or other qualified staff member will dispense bottles containing study drug (LAM-002A and placebo). Sufficient bottles will be dispensed to the subject to provide an adequate drug supply for the duration of the planned treatment course.

8.1.6. Return and Compliance Assessment

At each visit during the treatment course, empty, partially used, or full bottles of study drug (LAM-002A and placebo) should be retrieved from the subject. The quantities of unused study drug and the date when these study supplies are returned by the subject should be recorded in the study drug accountability records. In addition, at each visit the subject's dosing diary should be

reviewed, any incomplete or inconsistent entries should be addressed. Returned capsules and bottles may be destroyed according to the site's standard operating procedures (see Section 13.11).

8.1.7. Accountability

See Section 13.11 for information regarding study drug (LAM-002A and placebo) accountability.

8.1.8. Overdose Precautions

An overdose is defined as a dose taken (accidentally or intentionally) exceeding the overdose limit. In the case of a discrepancy in drug accountability, an overdose will be established only when it is clear that the subject has received an excess dose, or the investigator has reason to suspect that the subject has received an excess dose.

There are limited data on the effects of LAM-002A overdose. LAM-002A doses as high as 150 mg BID (300 mg QD) were administered in a prior Phase 1 study. The adverse effects were primarily nausea, vomiting, and/or diarrhea that occurred acutely and tended to be treatment-limiting.

For this protocol, an overdose of study drug is defined as ingestion of a total daily dose >300 mg QD (total daily dose) of LAM-002A (or the placebo equivalent). In a subject who experiences an overdose, consideration should be given as to whether study drug administration should be temporarily interrupted. If the overdose is recent and substantial, use of gastric lavage or induction of emesis may be considered but may not be necessary given the emetogenic nature of the drug at high doses. Observation for any symptomatic side effects should be instituted, and safety laboratory parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management should be instituted to mitigate adverse effects. The subject should remain under observation until adverse effects have recovered to baseline. There is no specific antidote for LAM-002A.

The medical monitor should be contacted if a study drug overdose occurs. The occurrence of an overdose does not preclude further protocol therapy if the subject appears to be safely benefiting from treatment and the circumstances that led to the initial overdose are unlikely to recur.

8.1.9. Inadvertent Exposure Precautions

Based on available data, LAM-002A is not expected to be acutely toxic, irritating, or genotoxic at levels that are likely to result from inadvertent exposure. However, personnel handling the drug should use reasonable precautions to avoid eye contact, skin contact, inhalation, or ingestion of study drug (LAM-002A or placebo). Subjects should be instructed to keep the drug secured such that it is out of the reach of children and is not inadvertently taken by others. The LAM-002A investigator brochure can be consulted for further information regarding exposure and spill precautions.

8.2. Study Drug Administration

8.2.1. Drug Administration

Study participants will be randomization in a 2:1 ratio to receive study therapy, comprising either LAM-002A, 125 mg (five 25-mg capsules/dose) or placebo capsules orally BID for the treatment period.

Subjects are to self-administer study drug (LAM-002A or placebo) starting on Day 1 and then continuously thereafter for the planned treatment course. Subjects should take the study drug at approximately the same time each day, ideally at ~12-hour intervals (e.g., ~8AM and ~8PM every day). Subjects will be provided a dosing diary to record daily dosing. Subjects may receive assistance from a caregiver for the completion of the diary.

In conjunction with pharmacokinetic assessments at all visits in Treatment Period A, after Screening, subjects should take the drug in a fasting state (defined as no food with the exception of clear liquids for ≥4 hours before and ≥2 hour after dosing) at the study center under the supervision of study personnel and the timing of study drug administration must be documented in the clinic notes and/or in the subject dosing diary. While variations in dosing schedule may occur in the outpatient setting, the prescribed regimen should be followed as closely as possible.

At each dose administration, the number of study drug (LAM-002A or placebo) capsules corresponding to the appropriate dose of each drug should be swallowed whole with 100 to 200 mL (~4 to 8 ounces) of water. Use of thickeners to help swallow the capsule is allowable. Subjects should be instructed not to bite or chew the capsules. In case of breakage of the capsules in the oral cavity, additional water should be taken as a rinse.

8.2.2. Fed/Fasting Status

At all study visits in Treatment period A, beyond the Screening Visit, study participants should ingest the study drug (LAM-002A or placebo) while fasting (defined as no food with the exception of clear liquids for ≥4 hours before and ≥2 hour after dosing). With other doses, subjects may take the study drug without regard to fed or fasting status.

8.2.3. Dose Schedule Interruptions and Vomited Doses

Subjects who have a delay in administration of <6 hours should take the planned dose as soon as possible after the intended time of administration. For subjects who have a delay in administration of ≥6 hours, the dose should not be taken. The planned timing of subsequent drug administration should not be altered.

For subjects who vomit shortly after taking the study drugs, the vomited dose should not be replaced. The planned timing of subsequent drug administration should not be altered.

8.2.4. Dose Modification Recommendations

If a subject experiences an AE that is suspected to be related to the study drug, appropriate monitoring, and supportive care (e.g., antiemetics, antidiarrheals) should be instituted consistent with the nature of the event.

If a subject experiences an intolerance to study drug that the investigator believes warrants dose modification, then the study drug administration should be interrupted until the toxicity recovers to Grade ≤1 or baseline. Subjects may then resume drug administration at the original dose level or at a reduced dose level of LAM-002A or placebo, 100 mg (four 25-mg capsules/dose) orally BID or placebo (four capsules/dose) orally BID. One further adjustments dose adjustment is permitted, to a reduced dose level of LAM-002A or placebo, 75 mg (three 25-mg capsules/dose) orally BID or placebo (three capsules/dose) orally BID. If the subject cannot tolerate study drug after a decrease in dose by 2 dose levels, then the subject should be discontinued from study drug therapy.

After the study drug dose is reduced, the dose should not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

Investigators may discuss modifications in the dosing regimen with the medical monitor.

8.3. Supportive Care

8.3.1. General Recommendations

Consistent with subject safety and comfort, administration of any prescription or over-the-counter drug products other than study medication will be minimized during the study period. Subjects should be discouraged from use of herbal remedies, self-prescribed drugs, tobacco products, or street drugs during their participation in the clinical study and should be counseled to minimize use of alcohol or nonmedical marijuana.

If considered necessary for the subject's well-being, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator. The investigator's decision to authorize the use of any drug other than study drug should take into account subject safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more significant underlying event, and whether use of the drug will compromise interpretation of study endpoints.

Subjects will be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed or over the counter) before and during the study.

Recommendations regarding specific types of concomitant therapies, supportive care, diet, and other interventions are provided below. To minimize variations in supportive care, the recommended supportive care agents should be considered unless there is a medical rationale in a specific subject for use of an alternative product.

8.3.2. Antibiotics, Antifungals, and Antivirals

Local practices or guidelines regarding infection prophylaxis may be followed. Subjects developing an intercurrent infection during study drug treatment may receive therapeutic antibacterial, antiviral, or antifungal drugs as needed. However, care should be taken to avoid or minimize concomitant administration of prophylactic or therapeutic antibacterial, antifungal, or antiviral, agents that are strong CYP3A4 inhibitors or inducers (see Section 8.3.8 and Section 15.1. Continuation of study therapy during treatment for an intercurrent infection is at the discretion of the investigator and medical monitor.

8.3.3. Anticoagulants

Use of local anticoagulation or antithrombotic agents to maintain a venous access catheter is permitted. However, for Treatment Period A, participants must not be currently taking anticoagulation and antiplatelet medications such as warfarin and clopidogrel bisulfate (Plavix™), that would be a contraindication to a lumbar puncture; aspirin and non-steroidal anti-inflammatories are allowed.

In addition, subjects who develop conditions that require anticoagulant therapy are permitted to receive such drugs and are not required to discontinue study participation.

8.3.4. Antidiarrheals

Subjects experiencing diarrhea (and/or abdominal cramping) may take loperamide at the earliest sign of a loose stool, an increase in bowel movements by 1 to 2 episodes compared to baseline, or an increase in stool volume or liquidity. The recommended regimen is 4 mg at the first onset of diarrhea, then 2 mg with each succeeding diarrheal stool until the subject is diarrhea-free for at least 12 hours.

Additional antidiarrheal measures may be implemented at the discretion of the investigator. Subjects should also be instructed to maintain oral fluid intake to help sustain fluid and electrolyte balance during episodes of diarrhea.

8.3.5. Antiemetics

If antiemetics are needed, it is recommended that subjects be offered granisetron (Kytril®, Granisol®), as an oral tablet or solution every 6 to 8 hours as needed. If subjects have persistent nausea or vomiting, consideration can be given to a 10-mg subcutaneous injection of the extended-release form of granisetron (Sustol®). Alternatively, application of a 31.3-mg granisetron transdermal patch (Sancuso®) every 3 to 7 days can be considered. For transdermal prophylaxis, 24 to 48 hours may be necessary to allow a sufficient period to achieve effective granisetron systemic concentrations. Use of the serotonin antagonists, ondansetron (Zofran®, Zuplenz®) or dolasetron (Anzemet®) is also permitted.

Aprepitant (Emend®) or netupitant+palonosetron (Akynzeo®) should be avoided because these drugs may inhibit CYP3A4 activity.

Benzodiazepines may be considered.

Corticosteroids can be introduced if other types of antiemetic agents are not sufficiently effective.

8.3.6. Antihistamine, Anti-inflammatory, or Antipyretic, Drugs

Antihistamines (e.g., cetirizine, diphenhydramine), and anti-inflammatory/antipyretic drugs (e.g., acetaminophen [paracetamol], nonsteroidal anti-inflammatory drugs [NSAIDs]), may be used during the study, as medically warranted.

8.3.7. Corticosteroids

Ongoing immunosuppressive therapy including systemic or enteric corticosteroids at screening or throughout the duration of the trial will be considered on a case-by-case basis, at the discretion of the site investigator and medical monitor.

8.3.8. Drugs with Drug-Drug Interaction Potential

While clinical data are not yet available, in vitro data suggest that LAM-002A is metabolized by CYP3A. Based on these findings, protocol candidates who require therapy with the strong CYP3A4 inhibitors or inducers listed in Section 15.1 should not be enrolled into the study.

During study participation, coadministration of study drug (LAM-002A or placebo) with the strong CYP3A4 inhibitors or inducers listed in Section 15.1 should be avoided, if possible. However, a subject who develops a condition that may require use of such drugs is not required to permanently discontinue study drug. If medically appropriate, investigators may wish to use a therapeutic alternative that would not be expected to affect these enzymes.

For subjects who require temporary use of a drug that does affect these enzymes (e.g., treatment with a systemic antifungal agent), study drug therapy can be temporarily interrupted and then resumed after completion of the CYP3A4 inhibitor. For subjects who require initiation of chronic therapy with a drug that strongly affects these enzymes, investigators must consult with the medical monitor to consider the best course of action. If subjects do receive a CYP3A4 inhibitor concomitantly with study drug, they should be monitored closely for signs of LAM-002A toxicity.

Of note, concurrent administration of LAM-002A and sodium phenylbutyrate/taurursodiol (Relyvrio™) will not be permitted given the potential for drug-drug interactions. Study subjects who initiate therapy with sodium phenylbutyrate/taurursodiol must permanently discontinue LAM-002A.

8.3.9. Drugs Known to Prolong the QT Interval

Available nonclinical and clinical data do not suggest a high risk that LAM-002A will alter the QT interval at doses of ≤125 mg BID. There is no specific restriction on use of drugs (e.g., antiemetics) that might prolong the QT interval.

8.3.10. Hematopoietic Support

Red blood cell or platelet transfusions may be administered as medically indicated.

8.4. Study Restrictions

8.4.1. Breast Feeding

There is no information regarding the presence of LAM-002A or its metabolites in human milk, the potential effects of the drug or its metabolites on the breastfed infant, or the potential effects of the drug or its metabolites on milk production. For these reasons, women who are nursing are

not eligible to participate in this study. Lactating women who do participate in this clinical trial must discontinue nursing during study therapy.

8.4.2. Contraception/Reproduction

In general toxicology studies, LAM-002A administration was not associated with adverse histopathological effects on organs of reproduction at exposures that are likely to be achieved clinically. However, no studies evaluating drug effects on reproductive function in animals or humans are available. Thus, subjects should be advised that the risks of LAM-002A for future reproduction are unknown.

No nonclinical data or clinical data are available regarding LAM-002A effects during embryo-fetal development. Accordingly, female subjects cannot be pregnant at the time of study entry and must be removed from study therapy if they do become pregnant.

Sexually active females of childbearing potential must agree to use a protocol-recommended method of contraception during heterosexual intercourse from the start of the screening period until ≥30 days after the final dose of study therapy. In the context of this protocol, a female subject is considered to be of childbearing potential unless she has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional laboratory postmenopausal range and a negative urine beta human chorionic gonadotropin [βHCG]); or is menopausal (age ≥50 years with amenorrhea for ≥6 months).

Sexually active male subjects who can father a child and are having intercourse with females of childbearing potential who are not using adequate contraception must agree to use a protocol-recommended method of contraception from the start of study therapy until ≥30 days after the final dose of the study therapy and to refrain from sperm donation from the start of study therapy until ≥90 days after administration of the final dose of study therapy. In the context of this protocol, a male subject is considered able to father a child unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy.

Protocol-recommended contraceptive methods are those that are considered highly effective (i.e., can achieve a failure rate of <1% per year when used consistently and correctly) [CTFG 2014]. Such methods include:

- Oral, intravaginal, or transdermal hormonal contraception that contains both estrogen and progestogen and is associated with inhibition of ovulation
- Oral, injectable, or implantable progestogen-only hormonal contraception that is associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomy or vasectomized partner with documented aspermia
- Sexual abstinence (i.e., refraining from heterosexual intercourse during the entire period of risk associated with the study drug administration considering that the reliability of sexual abstinence may be influenced by such factors as the duration of the clinical trial and the preferred and usual lifestyle of the subject)

It is advised that male subjects having heterosexual intercourse with a female partner of childbearing potential should use condoms plus an additional contraceptive method that together result in a failure rate of <1% per year. To avoid any potential study drug exposure to a partner, it is recommended that vasectomized men also wear condoms during sexual intercourse.

8.4.3. Diet

Because LAM-002A is a substrate of CYP3A4, subjects should be advised to avoid ingestion of grapefruit, grapefruit juice, or Seville oranges (which contains a potent CYP3A4 inhibitor) and should not use St. John's wort, which is a potent CYP3A4 inducer. No other specific dietary restrictions are required.

8.5. Duration of Study Drug Administration and Study Participation

In Part A of the study, subjects may receive study therapy (LAM-002A or placebo) up to Week 12. Subjects who complete the first 12 weeks on treatment will be eligible to receive active drug (LAM-002A capsules) for a further 12 weeks (OLE) up to Week 24.

In Part B of the study, subjects who complete Part A Week 24 on study drug, will be offered the opportunity to opt-in to continue to receive active drug for additional 36 weeks starting at the week 24 visit.

In Part C of the study, each subject can continue to receive LAM-002A as long as the subject, the investigator, and the study sponsor believe that study therapy is safely providing potential benefit.

However, the occurrence of any of the following events requires LAM-002A discontinuation:

- Subject request to withdraw from study treatment
- Intolerable study drug toxicity despite appropriate supportive care and/or dose modification
- The development of intercurrent illness or other substantial change in the subject's condition or circumstances that would place the subject at unacceptable risk as determined by the study investigator in consultation with the medical monitor
- Initiation of therapy with sodium phenylbutyrate/taurursodiol (Relyvrio™) or other therapies or interventions that would place the subject at unacceptable risk as determined by the study investigator in consultation with the medical monitor.
- Pregnancy or breastfeeding
- Inability to safely swallow study drug capsule at any time throughout the study
- Substantial noncompliance with study drug administration, study procedures, or study requirements in circumstances that increase risk or substantially compromise the interpretation of study results
- Discontinuation of the study by the study center, the study sponsor, relevant regulatory agencies, or the IRB/IEC

In Study Parts A and B, subjects who discontinue study therapy will complete an Early Termination visit as soon as possible. Discontinued subjects will also complete the Follow-Up Period of the study by completing the final Follow-up Telephone Call Visit, 4 weeks post their Early Termination Visit unless any of the following circumstances occurs:

- Subject request to withdraw from follow-up
- Subject lost to follow-up
- Subject death
- Termination of the study by the study center, the study sponsor, relevant regulatory agencies, or the IRB/IEC

9. SAFETY ASSESSMENT

9.1. Definitions

9.1.1. Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a medicinal product; the event does not necessarily have a causal relationship with study drug administration or usage. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

In this study, any of the following events will be considered an AE:

- Any complication that occurs as a result of a protocol-mandated procedure (e.g., venipuncture, ECG).
- Any preexisting condition that increases in severity or changes in nature during or as a consequence of study drug administration.
- Any injury or accident. If a medical condition is known to have caused the injury or accident (e.g., a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate AEs.
- Any abnormality in physiological testing or a physical examination finding that requires clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Any laboratory (e.g., clinical chemistry, hematology, urinalysis) or investigational abnormality (e.g., ECG, X-ray) independent of the underlying medical condition that requires clinical intervention, results in further investigation (beyond ordering a repeat [confirmatory] test) or leads to investigational medicinal product interruption or discontinuation unless it is associated with an already reported clinical event. If the laboratory abnormality is part of a syndrome, the syndrome or diagnosis (e.g., anemia) not the laboratory result (e.g., decreased hemoglobin) should be recorded.

A complication related to pregnancy or termination of a pregnancy (see Section 9.8.2 for additional information).

For the purposes of this study, symptoms of progression/worsening of ALS, including ‘normal’ progression, will be recorded as adverse events.

Measures of disease progression (e.g., ALSFRS-R score, VC) will not be recorded as adverse events even if they worsen (they are being recorded and analyzed separately).

None of the following events is considered an AE:

- Laboratory abnormalities not requiring clinical intervention or further investigation. Such abnormalities will be captured as part of laboratory monitoring.
- A diagnostic, medical, or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion). However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins

during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded in the source documents.

- A preexisting disease or condition or laboratory abnormality present or detected before the initial screening visit and that does not worsen.
- An intervention not associated with an untoward medical occurrence (e.g., hospitalization for elective surgery or for social and/or convenience reasons).
- An overdose without clinical sequelae.

9.1.2. Serious Adverse Event

An SAE is defined as an untoward medical occurrence that results in any of the following outcomes

- Death (i.e., all deaths, regardless of causality, occurring between the first administration of study drug to within 28 days after last study drug administration will be reported as SAEs). Death is not an SAE term; the reported SAE should be the event that caused the death. Death is the outcome of this SAE.
- Life-threatening situation (i.e., with an immediate risk of death from the event as it occurred but not including an event that, had it occurred in a more serious form, might have caused death).
- In-patient hospitalization or prolongation of existing hospitalization.
    - Of note, an untoward medical occurrence that occurs during hospitalization is an AE but a complication that prolongs hospitalization is an SAE. In-subject hospitalization comprises formal admission to a hospital for medical reasons, for any length of time, whether or not hospitalization extends overnight. However, hospital admissions or prolongations of hospitalization for administration of the study drug or procedures required by the study protocol, diagnostic observations or procedures, administration of concomitant or subsequent therapy for ALS, logistical issues (e.g., lengthy travel), or the convenience of the subject or clinical personnel are not considered serious.
    - An inpatient hospital admission in the absence of a precipitating, treatment-emergent, clinical adverse event may meet criteria for "seriousness" but is not an adverse experience, and will therefore, not be considered an SAE. An example of this would include a social admission (participant admitted for other reasons than medical, e.g., lives far from the hospital, has no place to sleep).
- Persistent or significant disability/incapacity.
- Congenital anomaly/birth defect.
- Other medically significant event. Such events may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the subject, or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events might include:
    - Allergic bronchospasm requiring intensive treatment in an emergency room or at home
    - New cancers or blood dyscrasias

- Convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

9.1.3. Unexpected Adverse Event

An unexpected AE is defined as an event that has a nature, severity, or specificity that is not consistent with the applicable investigator brochure, or that is symptomatically and pathophysiologically related to a known toxicity but differs because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed and reported rather than an experience that has not been anticipated based on the pharmacological properties of the study drug.

9.1.4. Treatment-Emergent Adverse Event

A TEAE is defined as an AE that occurs or worsens in the period from the first dose of study drug administration to 28 days after the last dose of study drug.

9.1.5. Adverse Events of Special Interest

There are no adverse events of special interest in this protocol.

9.2. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject should be questioned about AEs at each scheduled study center visit or during any telephone contact with the subject. The type of question asked should typically be open-ended, e.g. "Have you had any new health problems?" or a similar type of query.

9.3. Recording Adverse Events

All AEs will be assessed by the investigator or qualified designee and recorded in the electronic case report forms (eCRFs). The following considerations apply in collecting AE information:

- Recognized medical terms (not colloquialisms, abbreviations, or jargon) should be used when recording AEs. Ideally the description should be consistent with MedDRA nomenclature.
- The medical diagnosis (i.e., disease or syndrome) should be recorded instead of signs and symptoms (e.g., pneumonia instead of shortness of breath, coughing, and fever).
- Any sign or symptom considered as unrelated to an encountered disease or syndrome should be recorded as an individual AE (e.g., if nausea and severe headache are observed at the same time, each event should be recorded as a separate AE).

- If an AE resolves and reoccurs at a later date, a new AE must be documented and reported, as appropriate.

The following information should be recorded:

- Description as to whether the AE is serious, if applicable (see Section 9.1.2)
- The start date (date of AE onset)
- The stop date (date of AE resolution)
- The severity of the AE (see Section 9.5)
- A description of the relatedness of the AE to the study drug or to a study procedure (see Section 9.6)
- The action taken due to the AE
- The outcome of the AE

9.4. Coding of Adverse Events

The MedDRA® dictionary will be used to classify all AEs reported during the study by system organ class (SOC) and preferred term (PT).

9.5. Grading of the Severity of an Adverse Event

The severity of AEs will be graded and reported using the intensity grades as defined in Table 2.

Table 2. Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the subject's overall health and well-being, does not interfere with the subject's usual function, and is not likely to require medical attention.
Grade 2	Moderate	Sign or symptom causes interference with usual activity or affects clinical status and may require medical intervention.
Grade 3	Severe	Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up.
Grade 4	Life-threatening	Sign or symptom results in a potential threat to life.
Grade 5	Fatal	Sign or symptom results in death.

The distinction between the seriousness and the severity of an AE should be noted. Severity is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events (as listed in Section 9.1.2).

9.6. Describing Adverse Event Relationship to Study Drug and Study Procedures

The investigator will evaluate the causal relationship of each AE to a study drug and/or to a study procedure (e.g., venipuncture or ECG evaluation) and record that relationship on the appropriate CRFs. Causality will be assessed considering whether the AE is reasonably related to the study drug or procedure or whether the AE is not reasonably related to the study drug or procedure considering the definitions in Table 3.

Table 3. Relationship of Study Drug to Adverse Event

Relationship	Description
Definite	A clinical event in which a relationship to the use of the study drug seems definite because of such factors as consistency with known effects of the drug; a clear temporal association with the use of the drug; lack of alternative explanations for the event; improvement upon withdrawal of the drug (de-challenge); and recurrence upon resumption of the drug (rechallenge).
Probable	A clinical event in which a relationship to the study drug seems probable because of such factors as consistency with known effects of the drug; a reasonable temporal association with the use of the drug; lack of alternative explanations for the event; and improvement upon withdrawal of the drug (de-challenge).
Possible	A clinical event with a reasonable temporal association with administration of the study drug, and that is not likely to be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking.
Unlikely	A clinical event with a temporal relationship to study drug administration that makes a causal relationship improbable and for which other factors suggesting an alternative etiology exist. Such factors might include a known relationship of the clinical event to a concomitant drug, past medical history of a similar event, the subject's disease state, intercurrent illness, or environmental factors.
Unrelated	A clinical event in which a relationship to the study drug seems improbable because of factors such as inconsistency with known effects of the study drug; lack of a temporal association with study drug administration; lack of association of the event with study drug withdrawal or rechallenge; and/or presence of alternative explanations for the event. Alternative explanations might include a known relationship of the clinical event to a concomitant drug, past medical history of a similar event, the subject's disease state, intercurrent illness, or environmental factors.

9.7. Adverse Event Reporting Period

The start of the AE reporting for a study subject will coincide with the first administration of study drug for this study. After the first administration of study drug, all AEs (serious and nonserious, related and unrelated) should be reported. Unless a subject withdraws consent for follow-up, each subject must be followed until the end of the AE reporting period at Week 28 or when any ongoing drug-related AEs and/or SAEs have resolved or become stable. The investigator should use appropriate judgment in ordering additional tests as necessary to monitor the resolution of events. The medical monitor or the sponsor may request that certain AEs be followed longer.

Investigators are not obligated to actively seek information regarding the occurrence of new SAEs beginning after Week 28. However, if the investigator learns of such an SAE and that event is deemed relevant to the use of LAM-002A, he/she should promptly document and report the event. A longer reporting period applies in the case of pregnancy (see Section 9.8.2).

9.8. Study Center Reporting Requirements

9.8.1. Adverse Event Reporting Requirements

Classification of an event as serious or non-serious (see Section 9.1) determines the reporting procedures to be followed by the study center. Study center reporting requirements for AEs are summarized in Table 4.

Table 4. Study Center Reporting Requirements for Adverse Events

Classification	Reporting Time	Reporting Action
Serious	Within 24 hours of investigator site becoming aware of the event	Submit a SAE report on designated SAE report form to the sponsor (Study Part C) or designee (Study Parts A and B) [a]
	Per eCRF submission procedure	Record and submit information on appropriate eCRFs.
	Per eCRF submission procedure	Record and submit information on appropriate eCRFs.
Nonserious	Per eCRF submission procedure	Record and submit information on appropriate eCRFs.

[a]For Study Parts A and B, see contact information provided in the study safety manual. For Study Part C, SAEs should be reported directly to the sponsor at safety@ai-thera.com.
Abbreviations: eCRF=case report form; SAE=serious adverse event

For SAEs, a paper SAE report form must also be completed and submitted within 24 hours of the investigator site's first awareness of the event to the sponsor. For Part C, all requested supplementary documents (e.g., discharge summary, autopsy report) and relevant data (e.g., ECGs, laboratory tests, discharge summaries) must be emailed within 24 hours to safety@ai-thera.com.

Investigators must also submit written safety reports as required by the IRB/IEC within timelines set by local and regional regulations. The study site should retain documentation of the submission of expedited safety reports to the IRB/IEC, and their receipt. Study site personnel should not wait to receive complete information or the investigator's signature before notifying the sponsor (or designee) and the IRB/IEC of an SAE.

The following minimum information is required:

- Subject identification (i.e., subject number, sex, age)
- Description of the SAE (diagnosis preferred, symptoms, etc.)
- Study drug and causal relationship of the SAE to the study drugs or study procedures

- Investigator name

Collection of complete information concerning SAEs is extremely important. The information in the AE portion of the eCRF and the SAE report form must match or be reconciled. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms.

All available and relevant supporting documentation (e.g., progress notes, pertinent laboratory and diagnostic test results, discharge summaries) will only be provided upon request.
The subject's name, address, and other personal identity information should be obscured on any source documents (e.g., progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries). The subject's unique study number should be included on each page of any document provided.

The sponsor (or designee) will review SAE reports for missing information and send queries to the site for resolution as indicated. The study site is responsible for obtaining pertinent follow-up information missing from initial reports and forwarding the information within 24 hours of receipt to the sponsor (or designee). Follow-up information to the SAE should be clearly documented as "follow-up" in the SAE report form.

The original SAE form and any follow-up forms must be kept on file at the study site. An SAE is followed until it is considered resolved, it returns to baseline, is chronically ongoing, or explained otherwise by the principal investigator.

9.8.2. Pregnancy

Each female subject should be instructed to inform the investigator immediately if she becomes pregnant at any time between the administration of first study drug dose until 28 days after the last administration of study drug. If a female subject becomes pregnant during the treatment period of the study, they will be discontinued from study treatment. Similarly, a male subject should also be instructed to inform the investigator immediately if his female partner becomes pregnant during this same study period.

The investigator should counsel the subject regarding the possible effects of study drug exposure on the fetus and the need to inform the study center, the medical monitor, and the sponsor (or designee) of the outcome of the pregnancy.

Neither the pregnancy itself nor an induced elective abortion to terminate the pregnancy without medical reasons is considered an AE; such occurrences should be reported on the appropriate paper pregnancy report form. However, if the outcome of the pregnancy meets the criteria for classification as an SAE (i.e., spontaneous abortion, induced abortion due to medical reasons, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator should follow the procedures for reporting SAEs (i.e., report the event to the sponsor or designee and follow up by submission of the appropriate AE eCRFs (see Section 9.8.1).

Additional information about pregnancy outcomes that are classified as SAEs includes:

- Any spontaneous abortion, including miscarriage and missed abortion, will be reported as an SAE.

- An induced therapeutic abortion to terminate any pregnancy due to complications or other medical reasons will be recorded as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 1 month that the investigator assesses as possibly related to the in-utero exposure to the study drug should also be reported.
- In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (i.e., there is no required minimum follow-up of a presumably normal infant before the paper pregnancy report form can be completed).
- The "normality" of an aborted fetus can be assessed by gross visual inspection unless there are pre-abortion laboratory findings suggestive of a congenital anomaly, in which case pathologic examination should be requested.

Information regarding any pregnancy in a study subject or the female partner of a male subject must be documented on a paper pregnancy report form and forwarded to the sponsor (or designee) within 24 hours of becoming aware of the pregnancy. Monitoring of the pregnancy in both female study subjects and female partners of male study subjects should continue until the conclusion of the pregnancy. For female partners of male study subjects, such monitoring applies if the pregnancy occurs in the period from the subject's start of study drug until 28 days after the subject's last dose of study drug. The outcome of the pregnancy should be reported on the pregnancy outcome report form within 5 days of the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported to the sponsor (or designee).

The investigator must report any pregnancy within 24 hours of becoming aware of it using the paper Pregnancy Report Form. Follow-up information documenting the pregnancy outcome should be reported as follow-up on the same page Pregnancy Report Form. The site should submit the appropriate paper report form to the Safety contact according to the instructions provided in the Study-Specific Regulatory Binder by the CRO.

9.9. Sponsor Reporting Requirements

Each SAE or special situation report received from the investigator will be evaluated by the sponsor (or designee). The sponsor (or designee) will assess the seriousness of the event (see Section 9.1.2), the expectedness of the event (see Section 9.1.3), and the relationship to participation in the study (see Section 9.6). The sponsor (or designee) will also indicate whether there is concurrence with the details of the report provided by the investigator.

The sponsor (or designee) will provide information for reporting of suspected, unexpected, serious adverse reactions (SUSARs) to regulatory authorities worldwide consistent with relevant legislation or regulations, including the applicable US FDA CFR, the European Commission Clinical Trials Directive (2001/20/EC, and revisions), and other country specific legislation or regulations. SUSARs will be reported to regulatory authorities within 7 calendar days for life threatening and fatal events, or 15 calendar days for all others. These timeframes begin with the first notification of the event from the reporting investigator to the sponsor (or designee), which represents the start of the regulatory clock (Day 0).

The sponsor (or designee) will also provide all investigators with a safety letter describing the SUSAR. The information will be provided by e-mail within 15 calendar days from Day 0. Investigators will be requested to provide written notification of the event to the relevant IRB/IEC as soon as is practical and consistent with local regulatory requirements and local institutional policy.

10. LABORATORY AND OTHER ASSESSMENTS

10.1. Methods and Analytes

Samples to be obtained and parameters to be analyzed are indicated in Table 5.

General safety laboratory assays (serum chemistry and hematology,) will be performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified central laboratory using standard clinical pathology methods whereas urine pregnancy tests and urinalyses will be performed at Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories associated with the study centers.

For pharmacokinetic analyses, evaluation of LAM-002A blood concentrations will be performed using a validated assay at a contract laboratory designated by the sponsor. Biomarker and genetic testing will be performed by the sponsor or at contract laboratories designated by the sponsor.

Vital signs will be obtained using standard clinical equipment available at each study center. ECGs will be performed at the clinical sites using equipment provided by the sites and will be interpreted by the sites.

Table 5. Laboratory and Other Parameters to Be Assessed

Test/Procedure	Parameters
Laboratory – Safety	
Urine pregnancy test	Urine β-HCG
Serum chemistry	Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphorus, magnesium, total protein, albumin, ALT, AST, ALP, CK, LDH, total bilirubin, uric acid, creatinine clearance.
Hematology	Hematocrit, hemoglobin, erythrocyte count, absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, Platelet count
Infectious disease	HIV, Hepatitis B, Hepatitis C
Urinalysis	Albumin, bilirubin, blood, clarity, color, glucose, ketones, nitrate, pH, protein, specific gravity, urobilinogen, and WBC screen
Coagulation studies	INR/PT, PTT
Laboratory – Pharmacokinetic	
Plasma and CSF pharmacokinetics	Plasma LAM-002 concentrations (as assessed by validated bioassays) (Worldwide Clinical Trials Early Phase Services/Bioanalytical Sciences, LLC., 8609 Cross Park Dr., Austin, TX 78754.) Retention of plasma and CSF for potential metabolite analyses

Test/Procedure	Parameters
Laboratory – Biomarkers	
Peripheral blood, plasma, and CSF biomarkers	CSF and PBMC levels of poly (GP) dipeptide repeat proteins (DPRs) as assessed by bioassays
	Plasma and CSF levels of sGPNMB and neurofilament light chain (NfL) as assessed by bioassays
	Other target engagement and disease biomarkers might be assessed in CSF, plasma, or PBMCs via established assays
Laboratory – Genetic	
C9ORF72 repeat expansion	Screening labs will also include repeat testing for the C9ORF72 repeat expansion at a central lab

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CK=creatine kinase, LDH=lactate dehydrogenase

10.2. Efficacy Assessments

10.2.1. ALS Functional Rating Scale - Revised

The ALS Functional Rating Scale –Revised (ALSFRS-R) (Cedarbaum 1999) is a quickly administered (5 minutes) ordinal rating scale used to determine participants' assessment of their capability and independence in 12 functional activities. 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. 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 participant 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. All ALSFRS-R evaluators must be NEALS certified.

10.2.2. Slow Vital Capacity

The vital capacity (VC) will be determined using the upright slow VC (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 VCn/ is 10% or greater for the first 3 trials. Only the 3 best trials are

recorded on the CRF. 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.

*Exceptions to the requirement of NEALS evaluator certification and study-approved spirometer will be permitted with Sponsor approval if performed in a Pulmonary Function Lab as needed during the COVID-19 pandemic.

10.2.2.1. Training and Validation

All evaluators must be NEALS trained and certified to perform the ALSFRS-R and SVC assessments; specific certification requirements are outlined in the Manual of Procedures (MOP). Certification and training will be provided by the Barrows Outcome Center. Certification occurs via a formal evaluation of reliability and accuracy of performance of these measures. Repeat certification will be required on an annual basis for all outcome measures. It is strongly preferred that a single evaluator performs all measures throughout the study, as much as possible.

10.2.3. ALS-Cognitive Behavioral Scale

The ALS-Cognitive Behavioral Scale (ALS-CBS) (Wooley 2010) 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 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, family member or other informant during the same time that the patient completes the cognitive portion. The questionnaire typically takes about 2 minutes to complete. If a caregiver is not present, this section of the questionnaire will not be performed.

10.3. Biofluid Collection

All samples will be labeled with a code. The code will not include any identifiable information but will be linked to a specific participant, visit, and sample. There is no scheduled date on which the samples will be destroyed. Samples may be stored for research until they are used, damaged, decayed or otherwise unfit for analysis. Participants have the option of declining participation in this portion of the study at any time by withdrawing their consent to have their sample used. However, it will not be possible to destroy samples that may have already been used.

Any routine clinical safety samples (for pregnancy test, serum chemistry, and hematology) that are analyzed at the clinical laboratory at the study center will not be shipped to the central lab. These samples should not be stored and will be discarded promptly after analysis.

Other samples (CSF and plasma for pharmacokinetics; CSF, blood and plasma for biomarkers) will be collected, processed, stored, and shipped following the instructions outlined in a detailed clinical study laboratory manual.

These samples will be shipped to the sponsor or the contract analytical laboratories using a shipping service designated by the sponsor and as specified in the clinical study laboratory manual. For the duration of the sample analysis campaign, samples will be stored at these contract laboratory facilities or sent for long-term storage at a storage facility designated by the sponsor. Samples will be retained as described for study records (see Section 13.7).

As described for other study records (see Section 13.7), copies of data relating to body weight and height, vital signs, oxygen saturation, etc. will be retained on file at the study centers. The sponsor may request copies of primary ECGs or radiography images (redacted of subject personal identifying information) for storage at the company.

10.3.1. DNA Collection

All participants will provide a blood sample for deoxyribonucleic acid (DNA) extraction for genome sequencing during the Screening Visit. Samples will only be analyzed for genotyping and repeat testing for the C9orf72 expansion at a central lab as needed to confirm prior testing results for eligibility purposes. The DNA sample can be collected after the Screening Visit if a screening sample is not obtained for any reason, or the sample is not usable.

10.3.2. Blood Biomarker Sample Collection

All participants will provide blood samples for biomarker assessments.

10.3.3. Lumbar Puncture

For all participants, the lumber puncture will be performed to collect CSF at the Baseline, Week 4, Week 8, Week 12, and Week 24/ET Visits. Study staff should document the time of last study drug dose was administered. The SI 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 (Zetterberg, 2010). 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 had a headache lasting more than 5 days. No other local or generalized complications occurred.

The procedure must be performed by the SI or another licensed practitioner with experience and training in performing LPs and must be listed on the site delegation log. When possible, LPs should be performed with an atraumatic Sprotte needle to reduce the risk of post-LP headache.

10.4. Safety and Other Assessments

10.4.1. Vital Signs and Anthropometrics

Vital signs include weight in kg or lbs, systolic and diastolic blood pressure in mmHg, pulse rate (radial artery)/minute, respiratory rate/minute, and temperature in °C or °F. Height in cm or in 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.

10.4.2. Clinical Safety Laboratory Tests

All participants will have clinical safety laboratory tests at the designated visits outlined in the schedule of activities (Table 1**)**. SI may order additional local testing, if needed, to further assess an AE, an out-of-range safety laboratory value or if there is any suspicion that a participant may be pregnant, throughout the course of the study.

10.4.3. 12-Lead ECG

A standard 12-lead ECG will be performed for safety at the Screening Visit to determine eligibility and for safety as outlined in the schedule of activities. Tracings will be reviewed and interpreted locally by an ECG reader at the sites and a copy of the tracings will be kept on site as part of the source documents.

10.4.4. Physical Examination

A physical examination will be performed and recorded. The following systems will be examined: head/neck, eyes, ears, nose, and throat, cardiovascular, lungs, abdomen, musculoskeletal, central nervous system, extremities, and skin.

10.4.5. Neurological Examination

A neurological examination will be performed and recorded. Examination will include assessment of mental status, motor and sensory function, reflexes, and coordination/cerebellar function.

10.4.6. Columbia-Suicide Severity Rating Scale

The US FDA recommends the use of a suicidality assessment instrument that maps to the Columbia Classification Algorithm for Suicide Assessment (C-CASA). The C-CASA was developed to assist the FDA in coding suicidality data accumulated during the conduct of clinical trials of antidepressant drugs. One such assessment instrument is 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 participant's lifetime.

At all other visits, the Since Last Visit version of the C-SSRS will be administered. This version of the scale assesses suicidality since the participant'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 participant 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 participant's safety. The site must ensure that the participant is seen by a licensed physician (or other qualified individual as required by local institutional policy) before leaving the study site. The SI will determine whether the participant 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 the C-SSRS. All evaluators must be certified to perform the C-SSRS; specific certification requirements are outlined in the study operations manual. Certification is required prior to performing the C-SSRS.

11. EFFICACY ASSESSMENTS

11.1. Primary Endpoints

- Safety: Defined as the occurrence of serious and non-serious treatment-emergent adverse events (TEAEs) and clinically significant treatment-emergent abnormalities in clinical and laboratory values.
- Tolerability: Defined as the percentage of participants who complete 12 weeks on study treatment during the Core Study. Secondary measures of tolerability will consider completion of 12 weeks on open-label study treatment during the OLE.
- Changes in plasma and CSF levels of LAM-002 and its active metabolites from pre-treatment to near-peak samples (1h ± 30 minutes after dosing) while on treatment.

11.2. Secondary Endpoints

- Changes in plasma and CSF levels of the LAM-002A-induced biomarker sGPNMB.

11.3. Exploratory Endpoints

- Change in ALS Functional Rating Scale Revised (ALSFRS-R) total and domain scores
- Change in vital capacity (VC)
- Permanent assisted ventilation-free survival
- Change in ALS-Cognitive Behavioral Scale (ALS-CBS)
    - PD markers of neurodegeneration, gene expression, and target engagement in CSF, PBMCs, and plasma including but not limited to:
        - CSF and PBMC levels of poly (GP) dipeptide repeat proteins (DPRs).
        - Plasma and CSF levels of neurofilament light chain (NfL).

12. STATISTICAL CONSIDERATIONS

12.1. Statistical Hypotheses

Our overall objective is to evaluate the safety, tolerability, CSF penetrance, and biological effect of LAM-002A in people with C9ORF72-associated ALS (C9ALS).

12.2. Sample Size Determination

Power analyses are based on safety, tolerability, and biomarkers.

12.2.1. Safety

Using the calculation power = $1-(1-p)^n$, where p is the probability of an event and n is the number of subjects in a treatment arm, with 8 participants exposed to LAM-002A, we will have greater than an 80% probability of seeing at least one occurrence of any serious adverse event resulting from treatment with LAM-002A for which the expected frequency is at least 18% of exposed participants.

12.2.2. Tolerability

The primary measure of tolerability will be defined as the percentage of participants who complete 12-weeks on study treatment during the Core Study. If more than one third of the participants on LAM-002A (e.g., 3 or more of 8 participants assigned LAM-002A) cannot tolerate the study treatment, we will consider LAM-002A as dosed intolerable. Using that rule, there is less than a 5% probability that we would reject the treatment as intolerable if its true tolerability is greater than 89%, and there is greater than an 80% probability that we would declare the LAM-002A treatment intolerable if the true tolerability is less than 54%.

Tolerability during the OLE will be considered as a secondary measure. We will summarize the proportion of participants tolerant of LAM-002A over the first 12 weeks of exposure among all participants who receive at least one dose, combining data from participants initially randomized to LAM-002A in the Core Study and those exposed after cross-over during the OLE. We will also summarize the proportion of participants tolerant of LAM-002A over 24 weeks of exposure among those initially randomized to LAM-002A in the Core Study, censoring any participants who choose not to continue into the OLE.

12.2.3. LAM-002A-induced biomarker sGPNMB

Preliminary data on 2-week change in sGPNMB levels in the plasma from 19 subjects treated with LAM-002A indicate a mean and standard deviation after log[2] transformation of 0.64±0.53. Based on those estimates, integrating over their uncertainty, assuming that the signal-to-noise ratio is no worse for 12-week change, and based on 2:1 randomization, a sample size of 12 participants will provide 59% power to detect a significant treatment-dependent increase in the marker sGPNMB levels when testing at two-sided $p < 0.10$. Assuming no uncertainty in the estimated standard deviation of 0.53 after log[2] transformation, a sample size of 12 participants randomized 2:1 provides 89% power to detect a 2.0-fold treatment-dependent 12-week increase in sGPNMB levels when testing at two-sided $p < 0.10$.

12.3. Analysis Sets

12.3.1. As-Treated (AT) Sample

The as-treated (AT) sample includes all eligible participants who received at least one dose of study drug classified according to the treatment actually received. The AT sample will be used for primary analyses of both safety and pharmacodynamic response.

12.3.2. Per-Protocol (PP) Sample

The per-protocol (PP) sample includes all AT participants who did not have any major protocol deviations. The final determination of the exclusion of subjects from the PP sample will be made prior to the database lock.

12.4. Statistical Analyses

12.4.1. General Considerations

Safety, tolerability, and permanent assisted ventilation-free survival summaries will be presented as percentages. Assisted ventilation will be defined as permanent when non-invasive or invasive ventilation is used for >22 hours in a 24-hour period, for 7 consecutive days. Date started is the first day of the 7-day period. Descriptive summary statistics of blood and CSF levels of LAM-002 and its pharmacodynamic marker sGPNMB, and all secondary endpoint data and their change from baseline will be presented by treatment group and visit. At the conclusion of the study, the de-identified data will be delivered to the Biostatistics Center for analyses. Details of the planned analyses will be specified in a separate statistical analysis plan (SAP).

12.4.2. Baseline Characteristics.

Distributions of baseline demographic, clinical, and laboratory characteristics will be summarized by intervention group using means and standard deviations or medians and interquartile range for continuous variables and by counts and percentages for categorical variables. No inferential statistics will be calculated given that any observed difference is axiomatically due to chance.

12.4.3. Safety Analyses

12.4.3.1. Adverse Events

Safety will be assessed by the occurrence of serious and non-serious treatment-emergent adverse events (TEAEs) and clinically significant treatment-emergent abnormalities in clinical and laboratory values. MedDRA coded TEAEs will be summarized as counts of events and proportions of participants experiencing a given type of event by treatment group and overall during the Core Study and during the OLE. Safety data from the OLE will be summarized by tabulating over the first 12 weeks of exposure among all participants who receive at least one dose of LAM-002A, combining data from participants initially randomized to LAM-002A in the Core Study and those exposed after cross-over during the OLE and by tabulating safety

outcomes of participants over 24 weeks of exposure among those initially randomized to LAM-002A in the Core Study who choose to continue into the OLE.

Counts and proportions of participants experiencing TEAEs will also be summarized by severity, relatedness, and outcome. Participants will be classified according to the highest severity, relatedness, and outcome across all TEAE each participant experienced.

12.4.3.2. Laboratory Parameters

Clinical laboratory tests including biochemistry, hematology, and urinalysis will be performed as listed in Table 1, and at time points specified in the Schedule of Activities. Microscopic examination will be performed on abnormal findings. Listings of all clinical laboratory results will be provided with the abnormal values flagged with "L" (below normal range) and "H" (above normal range) for continuous parameters, and “P” (present or positive) for categorical parameters.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) for each clinical laboratory test (continuous variables) will be presented. Change from baseline to each follow-up visit will also be presented. For a given laboratory test, the last recorded value (scheduled or unscheduled), prior to the first dosing will replace any missing baseline value. Otherwise, unscheduled results will not be included in the summary tables. For categorical variable (urinalysis test), the number of participants (frequency and percentage) will be tabulated by results (e.g., negative, positive, trace). A summary table of shifts from baseline to study exit will be provided. Results from repeat tests will not be included in the summary statistics unless the repeat was required (and documented as such) due to technical reasons or an invalid initial result.

12.4.4. Tolerability

Tolerance of study drug will be summarized by frequency and percentage of participants who discontinue study drug due to an adverse event.

12.4.5. Plasma and CSF LAM-002 Levels

Changes in plasma and CSF levels of LAM-002 and its active metabolites from pre-treatment to near-peak samples (1h ± 30 minutes after dosing) while on treatment will be summarized by treatment group and visit by mean, standard deviation, geometric mean, median, and range.

12.4.6. Biomarker Analyses

Levels of biomarkers will be summarized as treatment- and visit-specific means, standard deviations, geometric mean, medians, and ranges. Levels will be analyzed in a shared-baseline, repeated-measures linear mixed model that includes fixed effects of visit and treatment x post-baseline visit interaction and unstructured covariance among repeated measures. Biomarker levels in plasma, CSF, and PBMCs will be log-transformed if right skewed prior to analysis and estimates back-transformed for reporting. Linear contrasts of least-square means will be used to estimate within-group changes from baseline and to compare change from baseline between active and placebo arms. The primary estimate will be the treatment-dependent difference in change from baseline to week 12 among all treated participants.

Inference for the primary biomarker of sGPNMB in the CSF will be based on a two-sided $p < 0.10$. Step-down Bonferroni-adjusted p-values and nominal comparison-wise p-values without correction for multiple comparison will be reported for all primary and secondary biomarkers.

12.4.7. Exploratory Clinical Endpoints

Analysis of exploratory clinical endpoints will use the same shared-baseline, repeated measures mixed model described for analysis of pharmacodynamic biomarkers.

12.4.8. Subgroup Analyses

Given the planned sample size, no subgroup analyses are planned.

12.4.9. Plan for Missing Data

The planned analysis of pharmacodynamic outcomes is valid under the assumption that missing data are missing at random (MAR). If dropout rates differ substantially between groups, sensitivity analysis may be performed to examine the robustness of conclusions of the primary analysis to missing data.

12.5. Interim Analyses

12.5.1. Interim Futility Analysis

The study will incorporate an interim analysis for safety and evaluation of LAM-002 CSF levels after 6 randomized subjects (4 on LAM-002A and 2 on placebo) have initiated treatment and have completed the Week 4 Visit. Recommendations from an independent Data Safety Monitoring Board (DSMB) will guide considerations for early termination or design adaptations. If there is no detectable level of LAM-002 or its active metabolites in the CSF, the DSMB may recommend early termination due to futility or recommend performing a second interim futility analysis after all 12 randomized subjects have completed the Week 4 visit. If detectable levels of LAM-002 or its active metabolites are present in the CSF in one or more study participants, the study will continue. During the analysis, participant follow-up will not be halted.

12.5.2. Interim Safety Analysis

At the discretion of the DSMB, subsequent interim safety reports will be reviewed with no more than 6 months between reviews if there are subjects still receiving study treatment. The DSMB will consider early stopping for excess mortality if mortality is significantly higher in the LAM-002A arm compared to placebo arm based on Fisher's exact test using a criterion for significance of a one-sided $p < 0.20$.

13. STUDY ADMINISTRATION AND RESPONSIBILTIES

13.1. General Investigator Responsibilities

The principal investigator must ensure that:

- He or she will personally conduct or supervise the study.
- His or her staff and all persons who assist in the conduct of the study clearly understand their responsibilities and have their names included in the relevant Study Personnel documents.
- The study is conducted according to the protocol and all applicable regulations.
- The protection of each subject's rights and welfare is maintained.
- Signed and dated informed consent and, when applicable, permission to use protected health information are obtained from each subject before conducting study procedures. If a subject withdraws permission to use protected health information, the investigator will obtain a written request from the subject and will ensure that no further data be collected from the subject.
- The consent process is conducted in compliance with all applicable regulations and privacy acts.
- The IRB/IEC complies with applicable regulations and conducts initial and ongoing reviews and approvals of the study.
- Any amendment to the protocol is submitted promptly to the IRB/IEC.
- Any significant protocol deviations are reported to the medical monitor, the sponsor, and the IRB/IEC according to the guidelines at each study center.
- eCRF pages are completed in a timely fashion.
- All SAEs are reported to the sponsor (or designee) within 24 hours of knowledge and to the IRB/IEC per IRB/IEC requirements.
- All safety reports are submitted promptly to the IRB/IEC.

13.2. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

13.3. Compliance with Ethical and Regulatory Guidelines

The investigator will ensure that this study is conducted in accordance with ICH guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. For studies conducted under a US IND, the investigator will ensure adherence to the basic principles of GCP as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50, 1998, and 21 CFR, Part 56, 1998.

This study is also subject to and will be conducted in accordance with 21 CFR, Part 320, 1993, "Retention of Bioavailability and Bioequivalence Testing Samples."

Because this is a "covered" clinical trial, the investigator will ensure adherence to 21 CFR, Part 54, 1998; a covered clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator in the trial. The investigator or sub-investigator agrees to notify the sponsor of any change in reportable financial interests during the study and for 1 year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol-defined activities.

13.4. Institutional Review Board/Independent Ethics Committee (IRB/IEC)

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB/IEC. Approval from the IRB/IEC must be obtained before starting the study and should be documented in a letter from the IRB/IEC to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval. A signed protocol approval page, a letter confirming IRB/IEC approval of the protocol and informed consent, and a statement that the IRB/IEC is organized and operates according to GCP and the applicable laws and regulations must be forwarded to the sponsor before screening subjects for the study. Additionally, study centers must forward a signed Form FDA 1572 (Investigator Obligation Form) to the sponsor before screening subjects for study enrollment.

Any modifications or amendments made to the protocol or informed consent document after receipt of the initial IRB/IEC approval must also be submitted to the IRB/IEC for approval before implementation. Only changes necessary to eliminate apparent immediate hazards to the subjects may be initiated prior to IRB/IEC approval. In that event, the investigator must notify the IRB/IEC, the medical monitor, and the sponsor in writing within 5 working days after implementation. If a change to the protocol in any way increases the risk to the subject or changes the scope of the study, then written documentation of IRB/IEC approval must be received by the sponsor before the amendment may take effect. Additionally, under this circumstance, information on the increased risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand, and sign any revised informed consent document confirming willingness to remain in the trial.

The investigator shall submit a progress report at least once yearly to the IRB/IEC and must provide a copy to the sponsor. As soon as possible after completion or termination of the study, the investigator will submit a final report to the IRB/IEC and to the sponsor. This report should include the dates of initiation and completion of the trial, a description of any changes in study procedures or amendments to the protocol, any deviations from the protocol, the number and type of subjects evaluated, the number of subjects who discontinued (and the reasons for

discontinuation), the number of subjects who completed the trial, and the results of the trial, including a description of any AEs. The sponsor will assist the investigator in the preparation of this report, as needed.

13.5. Informed Consent

The investigator, or a designee (designee must be listed in the relevant in the relevant study personnel documents), must explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in 21 CFR Part 50 and other applicable national and local regulations governing informed consent. Each subject must provide a signed and dated informed consent before enrollment into this study. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

A copy of the IRB/IEC-approved informed consent must be forwarded to the sponsor or designee for regulatory purposes.

13.6. Confidentiality

Every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this study drug, the investigator agrees to allow the IRB/IEC, representatives of the sponsor and its designated agents, and authorized employees of appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the study center records of all subjects enrolled into this study. This includes providing by fax, email, or regular mail de-identified copies of clinical, laboratory, ECG, radiology, pathology, and/or other test results when requested by the sponsor. A statement to this effect will be included in the informed consent and a permission form authorizing the use of protected health information will also be included.

In accordance with local and national subject privacy regulations, the investigator or designee must explain to each subject that in order to evaluate study results, the subject's protected health information obtained during the study may be shared with IRB/IECs, the sponsor and its designees, and regulatory agencies. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject. If a subject withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject and to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results. The sponsor will only use or disclose the subject's protected health information as defined in the informed consent document.

The investigator must assure that each subject's anonymity will be strictly maintained, and that each subject's identity is protected from unauthorized parties. Only subject initials, date of birth, and an identification code (but no subject names) should be recorded on any form or biological sample submitted to the IRB/IEC, to the sponsor or its designees (e.g., laboratories), or to regulatory authorities. However, sufficient information must be retained at the study center to permit sample data and data in the database to be connected with the unique subject number assigned to each study participant.

The investigator agrees that all information received from the sponsor, including but not limited to the study drug, the investigator brochure, this protocol, the eCRFs, and any other study information remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain.

13.7. Study Files and Retention of Records and Biological Samples

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified by the IRB/IEC, representatives of the sponsor and its designated agents, and authorized employees of appropriate regulatory agencies. These documents should be classified into at least the following 2 categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, the IRB/IEC and governmental approval with correspondence, signed informed consent documents, drug accountability records, staff curriculum vitae and authorization forms (e.g., Form FDA 1572), and other appropriate documents and correspondence pertaining to the conduct of the study.

The required source data referenced in the monitoring plan for the study should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender)
- Documentation that the subject meets eligibility criteria, e.g., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Participation in trial (including trial number)
- Trial discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug (including relevant drug dispensing information)
- Record of all AEs and other safety parameters (including start and end date, causality, and intensity)
- Concomitant medications (including start and end date and dose if relevant dose changes occur)
- Date of trial completion and reason for discontinuation, if applicable

All clinical study documents must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., the United States, Europe, or

Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified or for 15 years, whichever is longer. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the sponsor. The investigator must notify the sponsor and obtain written approval from the sponsor before destroying any clinical study records. The investigator will promptly notify the sponsor in the event of accidental loss or destruction of any study records. The sponsor will inform the investigator of the date that study records may be destroyed or returned to the sponsor.

The sponsor must be notified in advance and must provide express written approval of any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party.

If the investigator cannot guarantee this archiving requirement at the study center for any of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers outside of the study center so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the study center.

Biological samples retained by the investigator will be stored and maintained by the investigator until notification is received from the sponsor that the retained samples and records no longer need to be retained. The investigator must obtain written permission from the sponsor before disposing of any retained samples. The investigator should promptly notify the sponsor in the event of accidental loss or destruction of any study samples. With the permission of the sponsor, the retained samples may be transferred to an acceptable designee, such as another investigator, another institution, a contract laboratory, a contract storage site, or to the sponsor.

13.8. Subject Screening Log

The investigator must keep a record that lists all subjects who signed the informed consent (including those who did not undergo screening). For those subjects who declined to participate or were subsequently excluded from enrollment, the reasons for not enrolling in the study must be described.

13.9. Modifications of the Protocol or Informed Consent Documents

Protocol modifications, except those intended to reduce immediate risk to study participants, will be made only by the sponsor. All protocol modifications must be submitted to the IRB/IEC in accordance with local requirements. Except as noted in Section 13.4, IRB/IEC approval must be obtained before changes can be implemented.

Informed consent documents cannot be changed without prior approval by the sponsor and the study center IRB/IEC.

13.10. Case Report Forms

Authorized study center personnel will complete eCRFs designed for this study according to the completion guidelines that will be provided. An eCRF is required and must be completed for each enrolled subject, with all required study data accurately recorded such that the information

matches the data contained in medical records (e.g., physicians' notes, nurses' notes, study center charts, or other study-specific source documents). The investigator will ensure that the eCRFs are accurate, complete, legible, and completed in a timely fashion after each subject's visit. The investigator will ensure that source documents that are required to verify the validity and completeness of data transcribed on the eCRFs are never obliterated or destroyed. As required by the protocol, eCRFs should also be completed for those subjects who fail to complete the study (even during the screening period). If a subject withdraws from the study, the reason must be noted on the eCRF, and thorough efforts should be made to clearly document outcome.

The eCRFs for this study will exist within a web-based electronic data capture (EDC) system. After the investigator or the investigator's designees (e.g., research coordinators) have been appropriately trained, they will be given access to the EDC system and will enter the data required by the protocol into the EDC system. Any change of data will be made via the EDC system, with all changes tracked by the system to provide an audit trail.

The eCRF must be completed and signed by the principal investigator or sub-investigator (as appropriate) within a reasonable time period after data collection. This signature serves to attest that the information contained in the eCRF is true.

13.11. Study Drug Accountability

The disposition of all study drug (LAM-002A or placebo) should be documented from the time of receipt at the study center through subject administration. An investigational drug accountability log must be maintained for drug accountability. It is acceptable to use a protocol-specific form or a study center form that captures the relevant information. Within the drug accountability log, the responsible study center personnel must maintain accurate records of the receipt of all study drug (LAM-002A or placebo) shipped by the sponsor (or its designee), including, but not limited to, the date received, bottle number, amount received, pertinent details about the condition of the study drug upon receipt based on visual inspection, and the disposition of the drug (e.g., to storage). If a study drug shipment arrives damaged, or if there are any other complaints relating specifically to the drug, a product complaint should be emailed to the sponsor or the sponsor's representative. Study drug accountability records must also be maintained that include the subject number to whom the study drug is administered, and the date, quantity and bottle number of the study drug administered.

Study personnel must ensure that study drug is kept in a secure locked area with access limited to authorized personnel. The study drug must not be used outside the context of this protocol. Under no circumstances should the investigator or study center personnel supply study drug to other investigators, subjects, or clinics, or allow the study drug to be used other than as directed by this protocol without the prior authorization from the sponsor.

Depending upon the decision of the sponsor, remaining unused study drug supply will be returned to the sponsor or its designee after the study is completed or will be discarded or destroyed at the study center. After investigational product accountability has been performed, study drug disposal can occur per instructions provided by the sponsor. If the study drug is discarded or destroyed at the study center, standard institutional policy should be followed. At study initiation, the monitor will evaluate the study center's standard operating procedure for study drug disposal/destruction in order to ensure that it complies with sponsor requirements. At the end of the study, following final drug inventory reconciliation by the monitor, the study

center will dispose of and/or destroy all unused study drug supplies, including empty containers, per instructions provided by the sponsor. If the study center cannot meet sponsor requirements for disposal, arrangements will be made between the study center and the sponsor or its representative for destruction or return of unused study drug supplies.

All study drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study. Study drug accountability records must be readily available for inspection by the study monitor or other representatives of the sponsor or by regulatory authorities.

13.12. Monitoring

Representatives of the sponsor or its designee will monitor Parts A and B of this study until completion. Monitoring may be conducted through telephonic, web-based, or personal visits with the investigator and study center staff as well as any appropriate communications by email, regular mail, or fax. The monitor is responsible for routine review of the eCRFs, regulatory documentation and drug accountability logs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The purpose of monitoring is adherence to GCP, to ensure compliance with the protocol and maintenance of the high quality and integrity of the data.

In accordance with GCP, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

13.13. Inspections

The source documents for this trial must be made available to appropriately qualified personnel from the sponsor or its representatives, to IRB/IECs, and to regulatory authority or health authority inspectors as a part of their responsibility to protect human subjects in research. The investigator agrees to provide access to records, facilities, and personnel for the effective conduct of any inspection or audit to representatives of the sponsor and regulatory agencies. It is important that the investigator and relevant institutional personnel are available during monitoring visits and possible audits or inspections and that sufficient time is devoted to the process. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the sponsor immediately.

13.14. Data Management

Electronic data capture will be used to enter study data into eCRFs and to transfer the data into a study-specific electronic database. During the data collection process, automated quality assurance programs will be used to identify missing data, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be forwarded to the investigative study center for resolution. As appropriate, eCRFs, listings, tables, and SAS datasets will be provided to the study centers for review.

Quality assurance and quality control systems will be implemented and maintained according to written standard operating procedures to ensure that the data are generated, recorded, and

reported in compliance with the protocol, GCP, and applicable regulatory requirements. Data collection and storage systems will provide audit trail, security mechanisms, and electronic signature capabilities that meet the requirements of FDA Title 21 of CFR Part 11 regarding electronic records and electronic signatures.

Data security will be controlled through appropriate and specific restriction of access only to data and systems required by individual users to accomplish their roles in the data management process. Individual login and password protections will be employed at study centers and at the sponsor or its designee. The database will exist on physically secured servers. Data backups will be done regularly and will be stored in separate facilities. Printed documents relating to the study will be secured when not under review.

13.15. Clinical Trial Insurance

The sponsor will secure clinical trial insurance. An insurance certificate will be made available to the participating study centers before study initiation.

13.16. Communications with Regulatory Authorities

The sponsor (or its designee) will assume responsibility for interactions with the FDA and any other relevant regulatory authorities. The sponsor will maintain an IND for LAM-002A in support of the study in the US and will maintain similar regulatory applications with other regulatory authorities as required for conduct of the study. In fulfilling these responsibilities, the sponsor (or a designee) will collect and assemble all required regulatory documents (e.g., Form FDA 1572, investigator financial disclosure forms, protocol and protocol amendments, investigator brochures, informed consent documents, annual reports) as required by regulation. The sponsor (or a designee) will also assume responsibility for AE reporting to regulatory authorities (as described in Section 9.9).

13.17. Public Notification of Study Conduct

Consistent with Section 113 of the Food and Drug Modernization Act of 1997 (FDAMA) and to ensure meeting the requirement of the International Committee of Medical Journal Editors (ICMJE) as a condition of consideration for publication of study results, the sponsor will register this protocol at the ClinicalTrials.gov website (or equivalent). If the protocol is registered at ClinicalTrials.gov, the sponsor will appropriately update the information at the website relating to study design and conduct during the course of the study. In order to facilitate this process, investigators will need to supply the sponsor with appropriate contact information for study center personnel.

13.18. Study Reporting and Publication

The sponsor may make information obtained during this study available in order to further the scientific or business needs of the company or as required by law or regulation. In this regard, the sponsor may provide study information to private or public organizations (e.g., business partners, collaborators, consultants, CROs, investors, other physicians who are conducting similar studies, funding organizations, regulatory authorities, or other government authorities).

The results may also be used for papers, abstracts, posters, or other material presented at scientific meetings or published in professional journals or as part of an academic thesis.

The sponsor will prepare a clinical study report for submission to relevant regulatory agencies. The sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). An abbreviated report may be prepared in certain cases, as appropriate.

The sponsor intends that the data from this study will be presented and published. Because the data will ultimately be part of a multicenter clinical trial, data from all study centers will be pooled and analyzed for a primary publication of the study results. The sponsor will coordinate and prepare this primary publication. The investigator agrees that the primary publication, which will be coordinated by the sponsor, will be the first publication to present the pooled study results. Other ancillary publications or presentations relating to the pooled data from this study may be suggested by the investigator but can only be published with the express consent of the sponsor and the other investigators; such ancillary publications will also be coordinated by the sponsor.

After the primary publication, or if the primary publication is not published within 2 years of termination of the study, the investigator may freely publish or present the results of his or her work conducted under the clinical trial agreement, subject to providing the sponsor with the opportunity to review the contents of any proposed presentation, abstract, or publication about such work, including any results of this study, in advance of any presentation or submission for publication. Within that advance notice period, the sponsor may review the proposed publication to identify patentable subject matter and/or any inadvertent disclosure of its confidential information, which must be redacted from any final publication or presentation. If necessary, to permit the preparation and filing of patent applications, the sponsor may elect an additional review period. The durations of the review periods will be specified in contractual agreements between each study center and the sponsor.

In most cases, the principal investigators at the study centers with the highest accruals of eligible subjects and/or who have provided significant intellectual input into the study design, shall be listed as lead or senior authors on publications and presentations of study results. Sponsor clinical personnel, lead statistician, scientific personnel, or other staff members meeting the requirements for authorship may also be included in the list of authors. This custom can be adjusted upon mutual agreement of the authors and the sponsor.

13.19. Study Discontinuation

Both the investigator and the sponsor reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. The investigator will be responsible for notifying the relevant study center IRB/IEC. The sponsor will be responsible for notifying the appropriate regulatory authorities. In terminating the study, the investigator and the sponsor will assure that adequate consideration is given to the protection of the subjects' interests. As directed by the sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

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15. APPENDICES

15.1. Strong CYP3A Inhibitors and Inducers

Effect on CYP3A	Drug
Strong CYP3A Inhibitors	boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir), telithromycin, troleandomycin, voriconazole
Strong CYP3A Inducers	apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort

Abbreviation: CYP=cytochrome P450 enzyme

Reference: Food and Drug Administration (FDA). Drug development and drug interactions: Table of substrates, inhibitors, and inducers. 2020 Mar 10. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#4

15.2. Protocol Amendment History

15.2.1. Summary of Changes: Version 2 (22 February 2021)

15.2.1.1. Overall Rationale for the Amendment

This amendment included changes to the protocol to accommodate FDA requests, to remove inconsistencies between study sections, and to clarify elements of the study design.

15.2.1.2. Description of Changes

Section or Table Number	Description of Change	Brief Rationale
• Various sections	• Changes to protocol versions and dates were made. • Minor typographical, syntax, or formatting corrections were made. • Minor section ordering corrections were made.	To make appropriate editorial modifications
• List of Abbreviations • Section 6. Study Population • Section 6.2 Exclusion Criteria • Section 9.5 Grading of the Severity of an Adverse Event	• References to the CTCAE were removed.	To comply with a request from the FDA that the CTCAE not be used to grade the severity of adverse events.
• Section 3.2 Secondary Objectives • Section 4.2 Secondary Endpoints	• Evaluation of plasma and CSF changes in the LAM-002A-induced biomarker sGPNMB had previously been categorized as a primary objective/endpoint but were recategorized as a secondary objective/endpoint.	To acknowledge the provisional nature of sGPNMB as a biomarker of drug effect.
• Section 8.5 Duration of Study Drug Administration and Study Participation	• Descriptions of the duration of the primary randomized, blinded therapy period (through Week 12) and additional duration of optional open-label therapy (through Week 24) were corrected and the maximum duration of post-therapy follow-up (through Week 28) was described.	To clarify the intended durations of therapy during the blinded and open-label portions of the study and to indicate the duration of the follow-up period.
• Section 9.1.1 Adverse Event • 9.7 Adverse Event Reporting Period	• In Section 9.1.1, an inconsistency in the definition of the AE reporting period was removed and in Section 9.7, the definition of the AE reporting period was noted to extend from the first administration of study drug until the end of the AE reporting period at Week 28 or when any ongoing drug-related AEs and/or SAEs have resolved or become stable.	To clarify the definition of the maximum AE reporting period consistent with other sections of the protocol.

Section or Table Number	Description of Change	Brief Rationale
• Section 9.1.2 Serious Adverse Event	• The definition of a fatal SAE for the protocol was defined as a death occurring between signing of the consent form to within 28 days after last study drug administration.	To clarify the definition of a fatal SAE consistent with other evaluation periods in the protocol.
• Section 9.1.4 Treatment-Emergent Adverse Event	• The definition of a TEAE for the protocol was defined as an AE that occurs or worsens in the period from the first dose of study drug administration to 28 days after the last dose of study drug.	To clarify the definition of a TEAE consistent with other evaluation periods in the protocol.
• Section 12.5.1 Interim Futility Analysis	• The minimum number of subjects required for an interim analysis was designated as at least 12 subjects (8 on LAM-002A and 4 on placebo)	To specify the minimum number of subjects required for the interim analysis with greater precision.

15.2.2. Summary of Changes: Version 3 (19 July 2021)

15.2.2.1. Overall Rationale for the Amendment

This amendment included changes to the protocol to correct errors, remove inconsistencies between study sections, and clarify elements of the study design.

15.2.2.2. Description of Changes

Section or Table Number	Description of Change	Brief Rationale
• Various sections	• Changes to protocol versions and dates were made. • Minor typographical, syntax, or formatting corrections were made.	To make appropriate editorial modifications
• Study Personnel	• Removal of this section as sponsor personnel contact details will not be maintained or specified in the protocol.	This information can frequently change and will be found instead within other study documentation/manuals used by the site.
• Section 1: Protocol Synopsis & Schedule of Activities (Study Objectives) • Section 3: Study Objectives • Section 4: Study Endpoints • Section 11: Efficacy Assessments	• Moving the secondary objective/endpoint of evaluating the biological activity of LAM-002A as measured by disease biomarkers in CSF, PBMCs and plasma to exploratory objectives/endpoints.	The assays for these biomarkers are more for research purposes and exploratory in nature.
• Section 1: Protocol Synopsis & Schedule of Activities (Study Design) • Section 5.1 Study Design	• Number of subjects adjusted to be approximate.	To allow for potential minor over enrollment or drop-out of subjects.

Section or Table Number	Description of Change	Brief Rationale
• Table 1 Schedule of Activities	• Footnote 9 added to the assessment of "Administration of LAM-002A drug in clinic" for the Week 24 Final Study Visit/Early Termination Visit.	Clarification added that subjects who discontinue study treatment prior to Week 24 will not receive a dose in clinical at their Early Termination Visit.
• Table 1 Schedule of Activities • Section 4.3 Exploratory Endpoints • Section 10.1: Methods & Analytes • Table 5 Laboratory & Other Parameters to be Assessed • Section 10.3: Biofluid Collection • Section 12.2: Sample Size Determination • Section 12.2.3: LAM-002A Induced Biomarker sGPNMB • Section 12.4.6: Biomarker Analyses • Section 12.4.8: Subgroup Analyses	• Revisions made to the naming of laboratory assessments including the removal of the term "pharmacodynamics".	To allow for consistency in laboratory assessment names across the protocol, eCRFs and other study manuals. The lab assessments are more biomarker in nature as opposed to pharmacodynamic.
• Table 1 Schedule of Activities • Section 9.8.2: Pregnancies	• Removal of AE collection including pregnancies during Screening.	To make consistent across the protocol that AEs including pregnancies will be collected after the subject receives their first dose.
• Table 1 Schedule of Activities	• Removal of survival assessment.	This is not a separate assessment as death information is to be collected as part of the end of study details and adverse event assessments.
• Table 1 Schedule of Activities	• Addition of Subject Dosing Diary Dispensing & Review.	Added to be consistent with mention of this activity within text of the protocol.
• Table 1 Schedule of Activities • Section 8.4.2 Contraception/Reproduction • Section 10.1 Methods & Analytes • Table 5 Laboratory & Other Parameters to be Assessed	• Urinalysis and urine pregnancy testing to be performed by the site locally.	Clarification of which lab assessments to be done locally by the site and to correct inconsistencies across protocol for pregnancy test method of collection.
• Table 1 Schedule of Activities	• Clarification on what data points for PK sampling will be collected in the eCRF. Actual collection times versus the total amount of time will be collected to avoid calculation errors.	Clarification on what will be collected in eCRF.

Section or Table Number	Description of Change	Brief Rationale
• Section 4.2 Secondary Endpoints • Table 5 Laboratory & Other Parameters to be Assessed	• Removal of phosphorylated neurofilament heavy chain endpoint and corresponding lab assessment.	No longer being performed.
• Section 4.3 Exploratory Endpoints • Section 12.4.1: General Considerations	• Addition of footnote to define criteria for assisted ventilation.	Clarification added to define assisted ventilation.
• Section 5.1: Study Design • Section 8.5 Duration of Study Drug Administration & Study Participation	• Revisions to clarify those subjects who discontinue study treatment early will only need to complete the Early Termination visit as soon as possible as well as the final Follow-Up Visit.	To align with the visit schedule as seen in the Schedule of Activities.
• Section 5.3 Rationale for Study Design	• Removed second paragraph that outlines possible next steps after this study depending on results.	The paragraph was not relevant and unnecessary to include as part of the rationale for study design.
• 6.1 Inclusion Criteria • Section 10.2.2: Slow Vital Capacity	• Modified inclusion criteria # 7 to clarify that the pandemic exception was specifically related to COVID-19 and requires Sponsor approval.	Clarification provided to further outline requirements for acceptance of FVC.
• Section 6.2 Exclusion Criteria	• Modified exclusion criteria #12 to indicate the list of experimental therapies will not be in the MOP but maintained by the Medical Monitor.	The list of experimental therapies will constantly change as new studies start up. To avoid having to revise the MOP each time a trial starts, an active list instead will be kept with the medical monitor
• Section 8.1.6 Return & Compliance Assessment	• Changes to text made to indicate subjects will be returning any used or unused study drug bottles at each visit as opposed to the end of the treatment period of the study.	This will allow for better oversight of subject compliance and drug accountability.
• Section 8.1.6 Return & Compliance Assessment • Table 1 Schedule of Activities	• Changes made to clarify that subject dosing diaries will be returned at each visit instead of being photocopied.	Subjects will be provided a new dosing diary to complete at each visit so copies will not be necessary as they will return the original completed diaries at the next scheduled visit.
• Section 8.2.1 Drug Administration	• Clarification that subject dosing diaries can be completed with caregiver assistance.	Assistance from a caregiver due to nature of ALS may be necessary.
• Section 8.5 Duration of Study Drug Administration & Study Participation	• Additional criteria for treatment discontinuation added for inability to swallow study drug capsules.	To align with the inclusion criteria of the study that subjects must be able to swallow the study drug capsules throughout the duration of the study.

Section or Table Number	Description of Change	Brief Rationale
• Section 9.4: Coding of Adverse Events	• MeDRA version removed.	The most current version of MeDRA will be used as per the Data Management Plan.
• Section 9.8.1: Adverse Event Reporting Requirements • Section 9.9: Sponsor Reporting Requirements	• Multiple grammatical changes made as well as the removal of the requirement to provide source documents up front with SAEs as this will only be required upon request.	Clarifications made to align with SOP reporting requirements that will be followed for this study.
• Section 9.8.2 Pregnancy	• Updated requirements to report pregnancies within 28 days of last study drug administration as opposed to 30. • Clarification that reporting of pregnancies will be completed via a paper form.	Reporting time-period adjusted to align with the final follow-up visit, 28 days post the last study drug administration. This will enable sites to be able to verify this information during the telephone follow-up call more efficiently.
• Section 9.8.2 Pregnancy	• Clarification that pregnant subjects will be required to discontinue from study treatment.	To align with the requirements for treatment discontinuation as per section 8.5.
• Table 5 Laboratory & Other Parameters to be Assessed	• The addition of creatinine clearance was added to the assessments to be done as part of the serum chemistry.	The central lab will be providing creatinine clearance calculations as part of the serum chemistry assessments.
• Table 5 Laboratory & Other Parameters to be Assessed	• Removal of notation that bioassays for the biomarkers are validated.	The bioassays are not currently validated and are for research purposes.
• Section 10.3: Biofluid Collection	• Revisions made to indicate that lab codes for samples will not be entered into the eCRF. • Revisions to sampling requirements if local labs are used.	Revisions made to align with final design of eCRFs. In addition, in the event a sample needs to be processed at a local lab, the sample will no longer need to be retained.
• Section 10.3.1: DNA Collection	• Revised to indicate that DNA collection will occur at Screening and not Baseline as well as clarification on when samples will be analyzed,	To align with the Schedule of Activities that DNA samples are to be collected as Screening. In addition, to clarify that samples will only be analyzed for genotyping and repeat testing for the C9orf72 expansion at a central lab as needed to confirm prior testing results for eligibility purposes.
• Section 10.4.3: 12-Lead ECG	• Revision made to indicate that ECGs will be performed and interpreted locally.	A central ECG reader is not being used for this study.

Section or Table Number	Description of Change	Brief Rationale
• Section 12.5.1: Interim Futility Analysis • Section 12.5.2: Interim Safety Analysis	• Number of subjects clarified to be up to 12 subjects. • Clarification that enrollment will not be stopped during the performance of the interim futility analysis. • Moving of the details around subsequent interim DSMB reports to the correct section 12.5.2 on interim safety analysis.	Subject numbers for the interim futility analysis clarified to allow flexibility in such instances as a subject discontinuing prior to completing Week 4. In addition, clarification added to indicate that sites may continue to enroll their subjects during the interim futility analysis.

15.2.3. Summary of Changes: Version 4 (18 October 2021)

15.2.3.1. Overall Rationale for the Amendment

This amendment primarily focused on reducing the sample size of the study consistent with the exploratory nature of the trial. The change was made to permit earlier analyses of the data and completion of the study to determine if the primary objective had been met.

15.2.3.2. Description of Changes

Section or Table Number	Description of Change	Brief Rationale
• Various sections	• Changes to protocol versions and dates were made. • Minor typographical, syntax, or formatting corrections were made. • Minor section ordering corrections were made.	To make appropriate editorial modifications.
• Section 1. Protocol Synopsis & Schedule of Activities: Study Design • Table 1. Schedule of Activities • Section 5.1. Study Design • Section 10.3.3. Lumbar Puncture • Section 12.2.3. LAM-002A-induced biomarker sGPNMB	• Planned number of subjects was reduced from 36 subjects to 12.	Size of the study was reduced due to the exploratory nature of the study. This will allow for the earlier analyses of the data and completion of the study to determine if the primary objective has been met.
• Section 7.1. Randomization and Stratification	• Addition that randomization will now be by permuted blocks in a single stratum.	Change made due to decrease in sample size.
• Section 10.1. Methods and Analytes	• Clarification made to differentiate which safety laboratory analyses will be performed by the central lab versus the site's local lab.	Clarification made to align with the set-up of the central laboratory.
• Section 12.2.1. Safety	• Modification made to the number of subjects expected to have SAEs.	To account for the change in sample size from 36 to 12.

Section or Table Number	Description of Change	Brief Rationale
• Section 12.2.2. Tolerability	• Modification made to the number of subjects expected to be able to tolerate LAM-002.	To account for the change in sample size from 36 to 12.
• Section 12.2.3. LAM-002A-induced biomarker sGPNMB	• Modifications made to lower statistical powering.	To account for the decrease in sample size from 36 to 12.
• List of Abbreviations • Section 12.3.1. Intention to Treat (ITT) Sample • Section 12.3.2. Per-Protocol Sample (PP)	• ITT Sample removed and replaced by As-treated (AS) Sample.	To account for the change in sample size from 36 to 12.
• Section 12.3.3. Safety and Tolerability • Section 12.4.8. Subgroup Analysis	• Removal of this section.	No longer applicable due to the change in sample size from 36 to 12.
• Section 12.4.1. General Considerations • Section 12.4.3.1. Adverse Events • Section 12.4.4. Tolerability	• Statistical methods updated in these sections to reflect the reduction in the sample size.	To account for the change in sample size from 36 to 12.
• Section 12.4.3.2. Laboratory Parameters	• Minor typographical, syntax, or formatting corrections were made. • Minor error fixed for which sample value should be used in the event of a missing value.	To make appropriate editorial modifications and minor clarifications as needed.
• Section 12.4.5. Plasma and CSF LAM-002 Levels • Section 12.4.6. Biomarker Analyses	• Addition of geometric mean and that the primary estimate will be among all treated patients.	Minor clarifications needed.
• Section 12.4.9. Plan for Missing Data	• Sensitivity analysis modified to be optional.	To account for the decrease in sample size from 36 to 12.
• Section 12.5.1. Interim Futility Analysis	• Clarifications made that the futility analysis would be completed once all 12 subjects complete Week 4 and that follow-up of the patients will continue during the analysis.	To account for the change in sample size from 36 to 12.
• Section 12.5.2. Interim Safety Analysis	• Clarifications made that additional safety reviews would only occur if subjects are still taking study treatment.	It is expected that enrollment and treatment of subjects will be completed prior to when the first safety review would be required due to the decreased amount of time it will take to enroll 12 subjects.

15.2.4. Summary of Changes: Version 5 (17 January 2022)

15.2.4.1. Overall Rationale for the Amendment

This amendment clarified drug dispensing, compliance assessments, and accountability procedures in the schedule of activities and added an earlier futility analysis to the study design.

15.2.4.2. Description of Changes

Section or Table Number	Description of Change	Brief Rationale
• Table 1 Schedule of Activities	• Addition of Dispensing of Study Drug and Perform study drug compliance and accountability.	Added for further clarification on timing and to be consistent with mention of these activities within text of the protocol.
• Section 12.5.1. Interim Futility Analysis	• The futility analysis will now be completed earlier once 6 subjects complete the Week 4 visit with the option to have another futility analysis once all 12 subjects complete the Week 4 visit based on DSMB recommendations.	Allows for an earlier futility analysis due to the extended enrollment timelines expected.

15.2.5. Summary of Changes: Version 6 (25 May 2022)

15.2.5.1. Overall Rationale for the Amendment

This amendment allowed patients to optionally continue on study drug for up to 36 weeks after completion of the first 24 weeks of the trial.

15.2.5.2. Description of Changes

Section or Table Number	Description of Change	Brief Rationale
• Section 1 Protocol Synopsis	• Addition of Treatment Period B	To allow for subjects to continue on further treatment for up to 36 weeks on a compassionate basis
• Table 1 Schedule of Activities	• Addition of Treatment Period Part B.	To detail visit activities during 36 weeks open label extension and redefine End of visit Safety call for both Parts A and B
• Section 5.1. Study Design	• Participants who complete Part A Week 24 on study drug, will be offered the opportunity to opt-in to continue in an open label extension for additional 36 weeks	To address how data will be managed for the main study (Part A) as a consequence of the addition of a compassionate use extension (Part B)

Section or Table Number	Description of Change	Brief Rationale
	• The study sponsor will conclude Part-A of the study, will collate and verify all study data through an appropriate data cut-off date, and will perform an interim database lock for an interim study analysis of the Part A study data and preparation of a study report	
• Section 8.2.1 Drug Administration	• Insertion of additional text "Treatment Period A" for clarity	To limit the fasting requirement to in clinic study visits in Part A
• Section 8.2.2. Fed/Fasting Status	• Insertion of additional text "Treatment Period A" for clarity	To limit the fasting requirement to in clinic study visits in Part A
• Section 8.3.3. Anticoagulants	• Insertion of additional text "Treatment Period A" for clarity	To limit the use of anticoagulants to Part A
• Section 8.5 Duration of Study Drug Administration and Study Participation	• Insertion of text adding Part B	To extend the active treatment regimen to include the optional compassionate use extension (Part B).
• Section 10.4.2 Clinical Safety Laboratory Tests	• Insertion of text adding an out-of-range laboratory value as a reason for additional testing	To provide more flexibility to PI to assess safety

15.2.6. Summary of Changes: Version 7 (5 January 2023)

15.2.6.1. Overall Rationale for the Amendment

The study was amended to include Study Part C with the intent of allowing study participants who were tolerating open-label LAM-002A therapy in Part A or B of the study to continue open-label LAM-002A if they did not wish to transfer to commercially available therapy for ALS, sodium phenylbutyrate/taurursodiol (Relyvrio™) that had been approved by the FDA during the conduct of the study.

15.2.6.2. Description of Changes

Section or Table Number	Description of Change	Brief Rationale
• Section 1 Protocol Synopsis	• Addition of information regarding Study Part C	To describe the Part C conditions for study drug administration and discontinuation, restrictions relating to the concomitant use of sodium phenylbutyrate/taurursodiol. safety monitoring, study drug dispensing, collection of safety and drug accountability data, and provisions for study termination.

Section or Table Number	Description of Change	Brief Rationale
• Section 5 Study Design And Conduct; Section 5.1 Study Design; Section 5.1.2 Study Part C	• Addition of a information regarding Study Part C	To describe the Part C conditions for study drug administration and discontinuation, restrictions relating to the concomitant use of sodium phenylbutyrate/taurursodiol. safety monitoring, study drug dispensing, collection of safety and drug accountability data, and provisions for study termination.
• Section 8 Study Drug Information, Administration, and Support; Section 8.3 Supportive Care; Section 8.3.8 Drugs with Drug-Drug Interaction Potential	• Addition of a proscription against concurrent use of LAM-002A and sodium phenylbutyrate/taurursodiol	To emphasize the restriction on concurrent use of LAM-002A and sodium phenylbutyrate/taurursodiol due to drug-drug interaction potential.
• Section 8 Study Drug Information, Administration, and Support; Section 8.5 Duration of Study Drug Administration and Study Participation	• Addition of information on the permitted duration of LAM-002A administration in Part C of the study including the need for discontinuation of LAM-002A upon initiation of sodium phenylbutyrate/taurursodiol	To indicate the duration of LAM-002A administration in Part C of the study and to reemphasize the constraint against concurrent use of LAM-002A and sodium phenylbutyrate/taurursodiol.
• Section 9 Safety Assessment; Section 9.8 Study Center Reporting Requirements; Section 9.8.1 Adverse Event Reporting Requirements	• Insertion of information indicating that SAEs observed in Parts A and B of the study were to be reported to the sponsor's designee while in Part C of the study, SAEs were to be reported directly to the sponsor	To clarify the difference in SAE reporting requirements for Parts A and B of the study relative to the reporting requirements for Part C of the study.
• Section 13 Study Administration and Responsibilities; Section 13.12 Monitoring	• Modification of text to indicate that site monitoring of the study would be restricted to Study Parts A and B	To clarify the site monitoring plan for the study.
• Section 15.2.6 Summary of Changes: Version 7 (5 January 2023)	• Addition of tabular summary of changes resulting in Version 7 of the protocol document.	To explain the changes to the protocol in transitioning from Version 6 to Version 7.