Clinical Study Protocol

Protocol Title:	**A Phase II Randomized, Double-Blind, Placebo-Controlled, Study of LAM-002A for the Prevention of Progression of COVID-19**
Protocol Number:	**LAM-002A-CVD-CLN01**
Protocol Date:	**16 October 2020**
NCT:	**NCT04446377**

Clinical Study Protocol

Protocol Title	A Phase II Randomized, Double-Blind, Placebo-Controlled, Study of LAM-002A for the Prevention of Progression of COVID-19
Study Sponsor	AI Therapeutics, Inc. 530 Old Whitfield St Guilford CT, 06437
Investigational Product	LAM-002A
Protocol Number	LAM-002A-CVD-CLN01
Developmental Phase	Phase II
US IND Number	148521
Protocol Versions (Date)	Version 1 (22 June 2020) Version 2 (10 July 2020) Version 3 (31 August 2020) Version 4 (16 October 2020)

Confidentiality Statement

Study Personnel

Information regarding sponsor-designated study personnel are described in the Pharmacy Manual.

AI Therapeutics, Inc. Approval Page

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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.

Langdon L. Miller, MD

16 October 2020

Langdon L Miller, MD
Clinical Advisor
AI Therapeutics, Inc.

Date

Principal Investigator Approval Page

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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:

Table of Contents

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
API	Active pharmaceutical ingredient
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
AVPU	Alert, voice, pain, unresponsive
βHCG	Beta human chorionic gonadotropin
BID	Twice per day
BIPAP	Bilevel Positive Airway Pressure
BTK	Bruton tyrosine kinase
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CK	Creatine kinase
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximal plasma concentration
CMC	Chemical Manufacturing and Control
CNS	Central Nervous System
COA	Certificate of Analysis
COVID	Corona virus Disease
CRF	Case Report Form
CRO	Clinical research organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
CYP3A4	Cytochrome P450 3A4
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EBV	Ebola virus
ECG	Electrocardiogram
eCLCR	Estimated creatinine clearance
ECMO	Extracorporeal membrane oxygenation
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data system
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration

Abbreviation	Definition
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
GLP	Good Laboratory Practice
GP	Glycoprotein
h or hr	Hour
HDPE	High density polyethylene
HEPA	High-efficiency particulate air
HET	Heterogeneity of treatment effect
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography
IC_{50}	Inhibitory Concentration 50%
ICH	International Conference on Harmonization
ICU	Intensive care unit
IEC	Independent ethics committee
IFNγ	Interferon gamma
IIG	Inactive Ingredient
IL6	Interleukin 6
IL-10	Interleukin 10
IL-12	Interleukin 12
IL-23	Interleukin 23
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent to treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
LDH	Lactate dehydrogenase
MARV	Marburg virus
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
mg/kg	Milligram/kilogram
mg/kg/day	Microgram/kilogram/day
µg	Microgram
MH	Mantel-Haenszel
µg/mL	Microgram per milliliter
mL	Milliliter
mL/kg	Milliliter/kilogram
Msec	Millisecond
n	Number of Observations
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

Abbreviation	Definition
NDA	New Drug Application
NEWS	National Early Warning Score
NHL	Non-Hodgkins Lymphoma
NIOSH	National Institute for Occupational Safety and Health
nM	Nanomolar
NPCI	Niemann-Pick C1
NSAID	Nonsteroidal anti-inflammatory drugs
PAPR	Powered air-purifying respirator
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PI	Phosphatidylinositol
PI3P	Phosphatidylinositol 3-phosphate
PIKfyve	Phosphatidylinositol-3-phosphate- 5 kinase
PK	Pharmacokinetics
pM	Pico molar
PO	Per os (by mouth)
PP	Per protocol
PPE	Personal protective equipment
QD	Once a day
QRS	Combination of three of the graphical deflections seen on a typical electrocardiogram (ECG)
QT	Time of start of Q wave until end of T wave in the heart's electrical cycle
QTc	Corrected QT
QTcF	QTc by Fridericia
RBC	Red blood cell
RNA	Ribonucleic acid
RNAseq	RNA sequence analysis
RR	Respiratory rate, also risk ratio
RT-PCR	Reverse transcriptase polymerase chain reaction
SAC	Staphylococcus aureus Cowan I strain
SAE	Series Adverse Event
SAP	Statistical Analysis Plan
SARS	Severe acute respiratory syndrome
SARS-CoV	Severe acute respiratory syndrome corona virus
SD	Standard Deviation
SoA	Schedule of activities
SUSAR	Suspected unexpected serious adverse reactions
T 1/2	Elimination half-life
TBD	To be determined
TdP	Torsades de Pointes
TEAE	Treatment Emergent Adverse Event
TFEB	Transcription Factor EB

Abbreviation	Definition
Th1	T-helper lymphocyte type 1
TLR	Toll-like receptor
TLS	Tumor Lysis Syndrome
T_{max}	Time to maximum concentration
UK	United Kingdom
US	United States
vs.	Versus

1. PROTOCOL SYNOPSIS AND SCHEDULE OF ACTIVITIES

Study Title	A Phase II Randomized, Double-Blind, Placebo-controlled, Study of LAM-002A for the Prevention of Progression of COVID-19
Study Number	LAM-002A-CVD-CLN01
Investigational Medicinal Product	LAM-002A (Apilimod dimesylate capsules)
Clinical Phase	Phase II
Sponsor	AI Therapeutics, Inc. 530 Old Whitfield Street Guilford, Connecticut 06437

Study Objective(s)

Primary Objective:

- To evaluate the antiviral efficacy of LAM-002A in subjects with COVID-19 with a baseline viral load $>10^5$ copies/mL as measured by SARS-CoV-2 clearance as determined by a quantitative RT-PCR (qRT-PCR) test from nasopharyngeal samples at Day 4 (72 hours ± 4 hours after the first dose of the study drug).

Secondary Objective(s):

- To evaluate the safety and tolerability of LAM-002A administration in the treatment of subjects with mild COVID-19.
- To evaluate the efficacy of LAM-002A in preventing COVID-19 disease progression in subjects who have proven infection with the SARS-CoV-2 virus as determined by a validated test; disease progression is defined as the occurrence of any of the following:
  - Death at Day 28
  - Hospitalization at Day 28
- To evaluate change in COVID-19 clinical status, as defined by the ordinal scale, of subjects treated with LAM-002A compared to placebo at Day 28, in subjects who become hospitalized and continue LAM-002A/placebo treatment.
- To compare the proportion of subjects at or above 95% oxygen saturation (O_2 sat) between LAM-002A versus placebo treatment groups as measured on Days 1, 4, and 11.

Exploratory Objective(s):

- To potentially evaluate the pharmacokinetics of LAM-002A in subjects with mild COVID-19.
- To potentially evaluate the antiviral efficacy of LAM-002A in subjects with COVID-19 with a baseline viral load $>10^5$ copies/mL as measured by SARS-CoV-2 clearance as determined by qRT-PCR test from saliva samples at Day 4.
- To potentially evaluate the antiviral efficacy of LAM-002A in subjects with COVID-19 with a baseline viral load $>10^5$ copies/mL as measured by SARS-CoV-2 clearance as determined by a qRT-PCR test from saliva samples at Day 11.
- To potentially evaluate the antiviral efficacy of LAM-002A in subjects with COVID-19 with a baseline viral load $>10^5$ copies/mL as measured by SARS-CoV-2 clearance as determined by a qRT-PCR test from saliva samples at Day 28.
- To potentially evaluate the antiviral efficacy of LAM-002A in subjects with COVID-19 with a baseline viral load $>10^5$ copies/mL as measured by SARS-CoV-2 clearance as determined by a qRT-PCR test from saliva samples at all available days based on AUC analysis.
- To potentially evaluate the difference in proportion of subjects with a SARS-CoV-2 viral load <LLOQ between the LAM-002A and the placebo arm as measured by a qRT-PCR test from nasopharyngeal samples at Day 4.
- To potentially evaluate the effect of LAM-002A on target engagement biomarkers.
- To potentially evaluate the effect of LAM-002A on pro- and anti-inflammatory cytokine levels and target engagement biomarkers in COVID-19 subjects.
- To potentially evaluate viral resistance by comparing genomic sequence of SARS-CoV-2 before and after LAM-002A treatment.
- To potentially evaluate the effect of SARS-CoV-2 genetic variants on LAM-002A efficacy.
- To potentially evaluate the effect of germline DNA sequence polymorphisms on LAM-002A safety and efficacy.

Study Design:

This is a Phase II randomized, double-blind, placebo-controlled, clinical study to evaluate the efficacy of LAM-002A compared to placebo treatment in adults with a confirmed SARS-CoV-2 infection who are receiving standard supportive care in an outpatient setting.

Study eligibility will be assessed during screening. All study participants must sign a written informed consent and satisfy the inclusion and exclusion criteria for the study. Written documentation confirming SARS-CoV-2 infection via a validated test, medical history, and current medication will be assessed for each consenting participant at screening.

Study participants will be randomized in a 1:1 ratio, to receive study therapy (either LAM-002A, 125 mg [5 capsules/dose]) PO BID or placebo [5 capsules/dose] PO BID) for 10 days. Nasopharyngeal swabs for quantification of baseline viral load will be performed on Day 1, however, results will not be available before administration of treatment. Subjects who experience an AE considered to be related to study therapy may have a decrease in study dose to LAM-002A, 100 mg [4 capsules/dose]) PO BID or placebo [4 capsules/dose] PO BID).

After the start of treatment on Day 1, subjects will be followed at Days 4, 6, 8, 11, 22, and 28. Subjects can withdraw from the study therapy or study participation at any time.

The study will incorporate an interim safety analysis after the first 30 subjects (15 on LAM-002A and 15 on placebo) have completed treatment and have been followed up for 11 days post-first dose. Recruitment and randomization will continue while this analysis is conducted. An additional interim analysis will be conducted at 50% of total enrollment. Recruitment and randomization will continue while this analysis is conducted. Recommendations from an independent DSMB will be used for decision of early termination or design adaptations.

Primary analysis of antiviral efficacy will be conducted in the subgroup of randomized participants with a baseline viral load > 10^5 copies/mL. As existing data on viral load is preliminary, this baseline may be adjusted as detailed in the statistics section. Non-parametric and parametric statistical analysis will be conducted as appropriate. For the comparison of the LAM-002A active arm and the control arm for the primary endpoint and secondary endpoints of drug effect, appropriate methods will be employed. Baseline subject characteristics, study therapy administration/compliance, safety, supportive care administration, and pharmacokinetics will be analyzed descriptively.

Product Description:

LAM-002A (apilimod dimesylate) is a first-in-class inhibitor of phosphatidylinositol-3-phosphate 5-kinase (PIKfyve) that has demonstrated *in vitro* anti-viral activity against SARS-COV-2 infected cells.

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 capsules 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

Procedures	Screening [a]	Intervention Period [Days]										Follow-up Period [Days]			Early Termination
		1	2	3	4	5	6 Phone Visit	7	8 Phone Visit	9	10	11	22 Phone Visit	28	
	Visit Days (Window)	[b]			(72 hours ± 4 hours)								(±2)	(±2)	
General Eligibility/Safety Assessments															
Informed consent [c]	X														
Enrollment criteria [d]	X														
Demographics [e]	X														
Medical history [f]	X														
ECOG performance status [g]	X														
Height, weight [h]	X														
Vital signs/oxygen saturation (NEWS) [i]	X	X			X		X		X			X		X	X
AE review [j]	X	X			X		X		X			X	X	X	X
Concomitant medication review [k]	X	X			X		X		X			X	X	X	X
12-lead ECG [l]	X														
Enrollment, Randomization, Study Drug Administration															
Submit randomization form [m]	X	X													
Study drug administration in clinic [n]		X													
Dispensing of study drug [o]		X													
Self-administration of study drug by subject [p]		X	X	X	X	X	X	X	X	X	X				
LAM-002A return/compliance and diary check [q]					X		X		X			X			X
Laboratory/Disease Assessments															
Patient COVID-19 symptoms diary completed (r)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum or urine pregnancy test [s]	X														
Blood for DNA and RNA isolation [t]	X														
Nasopharyngeal swabs for viral load analysis and infectious disease diagnostic (Biofire or equivalent) [u]		X			X										
Saliva for SARS-CoV-2 viral load, sequence, and target engagement analysis [v]		X			X							X		X	
Blood for hematology [w]	X											X			X
Serum chemistry [x]	X											X			X
Blood for cytokine analysis/target engagement [y]		X			X							X			
Plasma for pharmacokinetics [z]		X										X			
Secondary clinical endpoint assessment [aa]														X	
See footnotes on next page															

Table 1: Schedule of Activities

Footnotes:
N***ote: For pharmacokinetic assessments to be performed at specified times postdose on Day 1, the acceptable margin for actual time is as follows for hours (± minutes): 1 (±15) and 2 (±15). For scheduled visits after Day 1, permitted visit windows are indicated in the table.***
a. The screening and baseline visits can occur on the same day. Day 1 of the study is the day the subject takes the first dose of study drug after randomization.
b. Hematology and serum chemistry collected during Screening need not be repeated on Day 1.
c. Written informed consent will be obtained before performance of any study procedures that are not part of routine medical care.
d. Adverse changes in inclusion/exclusion criteria before randomization should be discussed with the medical monitor before randomization. Optional confirmatory SARS CoV-2 rapid viral test for patients who do not have documentation of positive infection. These rapid SARS CoV-2 viral tests will be supplied by the site and only conducted after the ICF is signed.
e. Demographics to include sex, age, race, ethnicity.
f. Medical history to include recording of COVID-19 history, previous therapy for COVID-19, past and ongoing medical conditions, substance use (smoking, alcohol), and cardiovascular history.
g. Performance status will be assessed at Screening using the ECOG scale: Grade 1: Fully active, able to carry on all pre-disease performance without restriction; Grade 2: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work; Grade 3: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours; Grade 4: Capable of only limited self-care; confined to bed or chair more than 50% of waking hours; completely disabled. Cannot carry on any self-care; totally confined to bed or chair.
h. Height (in centimeters) and weight (in kilograms) will be obtained at Screening only.
i. Vital signs (respiratory rate, blood pressure, pulse, temperature, and oxygen saturation via pulse oximetry) will be obtained with the subject resting in a seated upright position while breathing room air or with supplemental oxygen (if required). National Early Warning Score (NEWS) score will be derived from respiratory rate, oxygen saturation, supplemental oxygen use, temperature, systolic blood pressure, heart rate, and AVPU (alert, voice, pain, unresponsive). Assessments will be performed on Day 1 (predose), Day 4, Day 11 and Day 28 during site visits.
j. AEs will be described using concise medical terminology, including whether the AE is serious, the date of AE onset, the date of AE resolution, the severity of the AE based on the CTCAE, Version 5.0, a description of relatedness of the AE to study drug or to a study procedure, the action taken due to the AE, and the outcome of the AE. AEs will be collected beginning once ICF is executed and include any changes from medical history. Day 6, Day 8, and Day 22 assessments will be done via telephone
k. Concomitant medication assessments should include information regarding all prescription, nonprescription, and alternative medications (health foods). Use of any other drugs intended as therapy for COVID-19 (e.g. antivirals, antimalarials, BTK inhibitors, anti-IL-6 antibodies) or supportive care (e.g. antidiarrheals, NSAIDs, antiemetics, supplemental oxygen) should be noted. Information on concomitant medications used during Screening or since the last assessment will be assessed on each designated day. Day 6, 8, and 22 assessments will be done via telephone
l. 12-lead ECG will be obtained with the subject resting in a supine position at Screening. An ECG obtained within 30 days prior to the Screening visit is acceptable.
m. At Screening, obtain a subject number. On Day 1, randomize the subject and obtain a study drug bottle number.
n. The first dose of blinded study drug (LAM-002A or placebo) will be administered to the subject in the study center (with recording of the date and actual clock time of the LAM-002A administration). Depending on the time of administration (AM vs PM), the follow-up visit times will be determined as AM or PM.
o. Study personnel will dispense the remainder of the 10-day supply of blinded study drug (LAM-002A or placebo) to the subject with instructions for self-administration at home.

Table 1: Schedule of Activities

p.	Study subjects will be given the blinded study drug (LAM-002A or placebo) after randomization and will self-administer continuously thereafter until the evening of Day 10 or the morning of Day 11 (20 total doses) depending on if the first dose is taken in the AM or PM on Day 1. On Day 1, subjects should ingest the study drug (LAM-002A or placebo) while fasting (defined as no food with the exception of clear liquids for ≥2 hours before and ≥1 hour after dosing). With other doses, subjects may take the study drug without regard to fed or fasting status, However, subjects should be advised to avoid ingestion of grapefruit, grapefruit juice, or Seville oranges, and should not use St. John's wort. 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). At each dose administration, 5 capsules of blinded study drug (equivalent to 125 mg of LAM-002A or placebo) should be taken. If a subject requires a dose modification for drug-related toxicity, 4 capsules of blinded study drug (equivalent to 100 mg of LAM-002A or placebo) should be taken. At each dose administration, all capsules should be swallowed whole with 100 to 200 mL (~4 to 8 ounces) of water. 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.
q.	Empty, partially used, or full bottles of blinded study drug (LAM-002A or placebo) will be retrieved from the subject and drug compliance will be assessed throughout the dosing period. In addition, the subject's dosing diary will be reviewed, any incomplete or inconsistent entries will be addressed, and the dosing diary will be photocopied.
r.	COVID-19 symptoms will be documented by the patient on the applicable diary every day and reviewed by the study staff on Day 1, Day 4, Day 6, Day 8, Day 11, Day 22, Day 28. Patients should be instructed to collect this data on their patient diary every day, at the same time they take their study drug, until study completion. Patients should be instructed to return the paper diary to each clinic visit for review by study personnel. A copy of the paper diary will be collected as part of the source documentation and the original returned to the subject until the next visit. The original diary will be collected at the day 28 visit. Sites should schedule all visits, including phone visits, as close as possible to the drug dosing time on Day 1 to ensure consistency when reviewing patient symptoms.
s.	Serum or urine pregnancy testing will be performed in women of childbearing potential only. Pregnancy testing should be performed at Screening.
t.	Blood for genomic DNA and RNA will be used to assess for polymorphisms in the patient and the virus that may affect safety or efficacy; to be collected at Screening.
u.	Nasopharyngeal swabs collection to determine SARS-CoV-2 viral load and possibly sequence, expression biomarkers of target engagement and infectious disease diagnostic (Biofire or equivalent) to be collected on Day 1 (immediately prior to the first dose) and then on Day 4. The Day 4 swab should be obtained as close to 72 hours (± 4 hours) after the Day 1 dose as possible.
v.	Saliva collection to determine SARS-CoV-2 viral load, and possibly sequence and expression biomarkers of target engagement to be collected on Day 1 (immediately prior to the first dose) and then on Day 4, Day 11, and Day 28. NOTE: The Day 4 sample should be obtained as close to 72 hours (± 4 hours) after the Day 1 dose as possible.
w.	Hematology to include hemoglobin, hematocrit, erythrocyte count, absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils; platelet count. Hematology testing should be performed on Day 1 (predose), and Day 11. NOTE: Hematology results obtained within 30 days prior to the Screening visit are acceptable for the Day 1 sampling requirement.
x.	Serum chemistry to include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium phosphorus, magnesium, total protein, albumin, ALT/SGPT, AST/SGOT, ALP, CK, LDH, total bilirubin, uric acid to be collected on Day 1 (predose) and Day 11. NOTE: Serum chemistry results obtained within 30 days prior to the Screening visit are acceptable for the Day 1 requirement.
y.	Blood to be split for plasma samples for cytokine analysis and cell pellet/PBMC for target engagement will be collected on Day 1 (predose), Day 4 and Day 11. PBMC collection is optional.
z.	Only a few sites will collect pharmacokinetic data. Blood for LAM-002A pharmacokinetics will be collected predose on Day 1 and at 1 hr. (± 15 min.) and 2 hr.(± 15 min.) postdose, and on Day 11 (12 hours post the last dose on Day 10) to be performed in a subset of subjects as defined in the laboratory manual. Patients participating in pharmacokinetics will take study drug on Day 1 while fasting (defined as no food with the exception of clear liquids for ≥2 hours before and ≥1 hour after dosing).
aa.	Documentation of whether the subject has died or become hospitalized due to COVID-19 disease; documentation of whether the subject is symptom-free on Day 28.

2. INTRODUCTION

In December 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus RNA was quickly identified in some of these subjects. This novel coronavirus has been designated SARS-CoV-2, and the disease caused by this virus has been designated COVID-19. Following exposure to SARS-CoV-2, a window of treatment opportunity to prevent progression of disease exists. After exposure, there is a ~5-day incubation period (range 1-14 days), after which most individuals (~80%) develop mild disease. However, in high-risk individuals, including those ≥65 years of age, or those with pre-existing medical conditions (e.g. chronic lung disease, heart disease, or vascular disease), there is significantly increased risk of development of severe COVID-19 requiring intensive supportive care and often resulting in death.

No vaccine prophylaxis exists for COVID-19 and only one antiviral agent, remdesivir, has been approved under emergency-use provisions for therapy of COVID-19. Remdesivir has modest activity and must be given intravenously (IV), thus limiting its utility for outpatient care of subjects with mild COVID-19 symptoms. Development of a well-tolerated, easy-to-administer oral therapy for treatment of subjects with COVID-19 could prevent disease progression and consequent morbidity, need for intensive care, and mortality.

2.1. Study Rationale

The enzyme phosphatidylinositol-3-phosphate 5-kinase (PIKfyve) is known to be responsible for viral entry into cells. LAM-002A is a clinically tested, orally bioavailable, specific PIKfyve kinase inhibitor with *in vitro* antiviral activity against Ebola (EBV), Marburg (MARV), and the coronaviruses MERS-CoV, SARS-CoV, and SARS-CoV-2 (Ou et. al, 2020, Nelson et al, 2017; Qiu et al 2018; Riva et al., 2020; Kang et al, 2020).

AI Therapeutics plans to conduct a Phase II randomized, double-blind, placebo-controlled, study of LAM-002A to test if LAM-002A can prevent the progression of COVID-19 in subjects with mild COVID-19.

The study will enroll men and women within 8 days of symptom onset, who are ≥18 years of age, have documented SARS-CoV-2 infection as confirmed by a positive validated test, and have mild disease appropriate for initial outpatient care.

The appropriate dose and safety of LAM-002A administration has been established through data from several clinical studies that enrolled more than 700 combined healthy subjects and subjects with inflammatory and malignant conditions (see LAM-002A IB V5). A dose-range-finding study of LAM-002A in subjects with hematological cancers indicated that LAM-002A was not well tolerated at doses of 150 mg BID due to the rapid onset of nausea, vomiting, and/or diarrhea that preclude compliance with therapy. However, when administered at 125 mg BID, the drug demonstrated anticancer efficacy, and was well tolerated with excellent compliance, over a period of 2 years. 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 subjects with COVID-19.

2.2. Background

2.2.1. LAM-002A Mechanism of Action

Viral entry into cells has been shown to occur through components of the endosomal network, including Rab9 GTPase, the endo/lysosomal cholesterol transporter Niemann-Pick C1 (NPC1) (Murray et.al; 2005; Carette et. al., 2011), and phosphatidylinositol-3-phosphate 5-kinase (PIKfyve) (Murray et.al; 2005; Carette et. al., 2011; Nelson et.al., 2017; Qiu et.al., 2018). 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 regulates endosome and lysosome biogenesis and intracellular trafficking, facilitating late-endosome-to-trans-Golgi vesicular transport. This vesicular transport is part of the endosomal network that viruses use to enter the cell and replicate, suggesting PIKfyve inhibition can inhibit viral entry into cells and decrease viral replication.

LAM-002A is a first-in-class inhibitor of PIKfyve with an IC_{50} of 14nM, and K_d of approximately 75 pM (range 69-81 pM). The potential of LAM-002A to inhibit coronavirus viral entry has been tested *in vitro*. Apilimod potently blocked the entry of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) pseudotyped virus at all concentrations tested (62.5-250 nM) which has been independently replicated by Ou et.al., 2020. Importantly apilimod also blocked the entry of lentiviral pseudovirions expressing the SARS-CoV-2 S glycoprotein and displayed activity against several independent clinical isolates of SARS-CoV-2 (Ou et. al., 2020; Riva et al, 2020; Kang et al, 2020). Furthermore, combinatorial activity was observed with remdesivir suggesting that greater antiviral efficacy may be achieved with apilimod in combination with other anti-viral agents. Taken together, the effect on endolysosomal trafficking and in vitro anti-viral activity indicate that LAM-002A, the dimesylate salt of apilimod, has promising therapeutic potential for treating SARS-CoV-2 infections.

LAM-002A has also been found to potently inhibit the production of T-helper lymphocyte type 1 (Th1) cytokines IL-12 and IL-23 in PBMCs when treated with multiple toll-like receptor (TLR) stimuli (LAM-002A IB V4). In addition, LAM-002A inhibits IL-6 in response to IFN-γ/SAC (Wada et.al, 2007). Significant reduction of IL-12 and IL-23 transcripts, with a simultaneous increase in IL-10 was also observed in the skin lesions of psoriatic subjects treated with apilimod at 70 mg of apilimod free base QD (Wada et.al, 2012). While the stimuli and role of specific cytokines in COVID-19 are not known, these data suggest that LAM-002A has the potential to repress pro-inflammatory cytokines (e.g. IL-12, IL-23) and induce anti-inflammatory cytokines (e.g. IL-10).

2.2.2. Human Experience with LAM-002A

In addition to its anti-viral mechanism of action, the study rationale for LAM-002A in subjects infected with SARS-CoV-2 is based on the well-established safety and tolerability profile of the molecule in human trials.

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). To date, >700 study subjects have received apilimod dimesylate or apilimod, including 186 healthy subjects participating in clinical pharmacology studies, 468 subjects with nonmalignant inflammatory conditions (psoriasis, rheumatoid arthritis, Crohn's disease), and 62 subjects with B-cell hematological cancers.

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.

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-002A (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 COVID-19 or SARS-CoV-2 exposures evaluated to date, and the risk/benefit of LAM-002A in COVID-19 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.

No vaccine prophylaxis exists for SARS-CoV-2 infection and only one antiviral agent, remdesivir, has been approved under an emergency-use authorization for therapy for COVID-19. Remdesivir has modest activity and must be given intravenously (IV), thus limiting its utility for outpatient care of subjects with mild COVID-19 symptoms. While anti-viral efficacy of LAM-002A has not been established in humans or in animal models, the in vitro anti-viral activity suggests it may have potential efficacy in humans. Development of a well-tolerated,

easy-to-administer oral therapy for treatment of subjects with COVID-19 could prevent disease progression and consequent morbidity, the need for intensive care, and mortality.

A planned interim analysis with DSMB review early in the trial after 15 subjects in each treatment arm have completed treatment ensures the mitigation of any unanticipated safety risk in this COVID-19 population.

3. STUDY OBJECTIVES

3.1. Primary Objective

- To evaluate the antiviral efficacy of LAM-002A in subjects with COVID-19 with a baseline viral load $>10^5$ copies/mL as measured by SARS-CoV-2 clearance as determined by a qRT-PCR test from nasopharyngeal samples at Day 4 (72 hours ± 4 hours post the first drug dose)

3.2. Secondary Objectives

- To evaluate the safety and tolerability of LAM-002A administration in the treatment of subjects with mild COVID-19.
- To evaluate the efficacy of LAM-002A in preventing COVID-19 disease progression in subjects who have proven infection with the SARS-CoV-2 virus as determined by a validated test; disease progression is defined as the occurrence of any of the following:
  - Death at Day 28
  - Hospitalization at Day 28
- To evaluate change in COVID-19 clinical status, as defined by the ordinal scale, of subjects treated with LAM-002A compared to placebo at Day 28, in subjects who become hospitalized and continue LAM-002A/placebo treatment.
- To compare the proportion of subjects at or above 95% oxygen saturation (O_2 sat) between LAM-002A versus placebo treatment groups as measured on Days 1, 4, and 11.

3.2.1. Safety and Tolerability

- To evaluate the safety and tolerability of LAM-002A administration in the treatment of subjects with COVID-19.

3.2.2. Clinical Efficacy

- To evaluate the efficacy of LAM-002A in preventing COVID-19 progression in subjects who have proven infection with the SARS-CoV-2 virus as determined by a validated test; disease progression is defined as the occurrence of any of the following:
  - Death at Day 28
  - Hospitalization at Day 28

3.2.3. Clinical Status

- To evaluate change in COVID-19 clinical status as defined by the ordinal scale of subjects treated with LAM-002A compared to placebo at Day 28, including the subjects who become hospitalized and continue LAM-002A/placebo treatment.

3.2.4. Oxygen Saturation

- To compare the proportion of subjects at or above 95% oxygen saturation (O2 sat) between LAM-002A versus placebo treatment groups as measured on Days 1, 4 and 11.

3.3. Exploratory Objectives

3.3.1. Pharmacokinetic

- To potentially evaluate the pharmacokinetics of LAM-002A in subjects with mild COVID-19.

3.3.2. Viral Clearance

- To potentially evaluate the antiviral efficacy of LAM-002A in subjects with COVID-19 with a baseline viral load $>10^5$ copies/mL as measured by SARS-CoV-2 clearance as determined by a qRT-PCR test from saliva samples at Day 4.
- To potentially evaluate the antiviral efficacy of LAM-002A in subjects with COVID-19 with a baseline viral load $>10^5$ copies/mL as measured by SARS-CoV-2 clearance as determined by a qRT-PCR test from saliva samples at Day 11.
- To potentially evaluate the antiviral efficacy of LAM-002A in subjects with COVID-19 with a baseline viral load $>10^5$ copies/mL as measured by SARS-CoV-2 clearance as determined by a qRT-PCR test from saliva samples at Day 28.
- To potentially evaluate the antiviral efficacy of LAM-002A in subjects with COVID-19 with a baseline viral load $>10^5$ copies/mL as measured by SARS-CoV-2 clearance as determined by a qRT-PCR from saliva samples at all available days based on AUC analysis.
- To potentially evaluate the difference in proportion of subjects with a SARS-CoV-2 viral load <LLOQ between the LAM-002A and the placebo arm as measured by a qRT-PCR test from nasopharyngeal samples at Day 4.

3.3.3. Pharmacodynamic Objectives

- To potentially evaluate the effect of LAM-002A on target engagement biomarkers.
- To potentially evaluate the effect of LAM-002A on pro- and anti-inflammatory cytokine levels in plasma of COVID-19 subjects.

3.3.4. Genetic Evaluation Objectives

- To potentially evaluate viral resistance by comparing genomic sequence of SARS-CoV-2 before and after LAM-002A treatment.
- To potentially evaluate the effect of SARS-CoV-2 genetic variants on LAM-002A efficacy.
- To potentially evaluate the effect of germline DNA sequence polymorphisms on LAM-002A safety and efficacy.

4. STUDY ENDPOINTS

4.1. Primary Endpoint

- The primary efficacy outcome measure evaluates change in SARS-CoV-2 viral load at Day 4 from Day 1, of LAM-002A or placebo-treated subjects. SARS-CoV-2 viral load will be measured by a qRT-PCR test of nasopharyngeal samples. Analysis will focus on $\log_{10}$ viral load on Day 4 compared to baseline viral load at Day 1 in subjects with baseline viral load $>10^5$ copies/mL.

4.2. Secondary Endpoints

4.2.1. Safety and Tolerability

- The proportion of LAM-002A-treated subjects who develop TEAEs compared to placebo.

4.2.2. Clinical Efficacy

- The proportion of subjects treated with LAM-002A compared to placebo, who have disease progression by Day 28 as defined by the occurrence of:
  - Hospitalization
  - Death

4.2.3. Clinical Status

- Change in COVID-19 clinical status as defined by the ordinal scale, of subjects treated with LAM-002A compared to placebo at Day 28, in subjects who become hospitalized and continue LAM-002A/placebo treatment, based on the following scores:
  1. Not in the hospital
  2. Hospitalized, requiring low flow supplemental oxygen (such as nasal cannula)
  3. Hospitalized, not on invasive ventilation (such as 100% non-rebreather, BIPAP), (pre-ICU)
  4. Hospitalized, in the ICU, on invasive ventilation or ECMO
  5. Dead

4.2.4. Oxygen Saturation

- Proportion of subjects at or above 95% oxygen saturation (O2 sat) between LAM-002A versus placebo as measured on Days 1, 4, and 11.

4.3. Exploratory Endpoints

4.3.1. Pharmacokinetics

- Plasma concentration time profile of LAM-002A, on Day 1 pre-dose, at 1 (± 15 min) and 2 (± 15 min.) hr, and at trough on Day 11 will potentially be determined in a subset of subjects (target 20 subjects) to evaluate the deviation of pharmacokinetic parameters from expected exposure, and correlation of pharmacokinetic parameters with safety and efficacy.
- Maximum observed concentrations within the bounds of the sampling time points and trough concentration on Day 11.

4.3.2. Viral Clearance

- Change from baseline (Day 1, Pre-dose) of SARS-CoV-2 viral load as measured by a qRT-PCR test from saliva samples on Day 4, compared between the LAM-002A arm and the placebo arm in subjects with a baseline viral load $>10^5$ copies/mL.
- Change from baseline (Day 1, Pre-dose) of SARS-CoV-2 viral load as measured by a qRT-PCR test from saliva samples on Day 11, compared between the LAM-002A arm and the placebo arm in subjects with a baseline viral load $>10^5$ copies/mL.
- Change from baseline (Day 1, Pre-dose) of SARS-CoV-2 viral load as measured by a qRT-PCR test from saliva samples on Day 28, compared between the LAM-002A arm and the placebo arm in subjects with a baseline viral load $>10^5$ copies/mL.
- Difference in SARS-CoV-2 viral load as measured by a qRT-PCR test from saliva samples based on $AUC_{(Day1\text{-}Day11)}$, between the LAM-002A arm and the placebo arm in subjects with a baseline viral load $>10^5$ copies/mL.
- Difference in SARS-CoV-2 viral load as measured by a qRT-PCR test from saliva samples based on $AUC_{(Day1\text{-}Day28)}$, between the LAM-002A arm and the placebo arm in subjects with a baseline viral load $>10^5$ copies/mL.
- Difference in proportion of subjects with a SARS-CoV-2 viral load <LLOQ as measured by a qRT-PCR test from nasopharyngeal samples between the LAM-002A and the placebo arm at Day 4.

4.3.3. Pharmacodynamics

- Changes in the expression of target engagement biomarkers in the nasal epithelium, PBMCs, and plasma.

4.3.4. Immunogenicity Endpoints

- Changes in plasma levels of IL-12, IL-23, and IL-6, IFN-γ, IL-10 and GM-CSF (additional cytokines may be analyzed in parallel).

4.3.5. Genetic Endpoints

- Changes in viral genome sequence before and after LAM-002A treatment.

- Effect of SARS-CoV-2 genetic variants on efficacy (% of subjects that progress per variant), as determined by viral genome sequencing.
- Effect of genetic polymorphisms on LAM-002A safety and efficacy.

5. STUDY DESIGN AND CONDUCT

5.1. Study Design

This is a double-blind, randomized, placebo-controlled Phase II study for the treatment of SARS-CoV-2 positive outpatient individuals with LAM-002A. The study will compare the active arm of LAM-002A plus standard of care, with the control placebo arm plus standard of care. This study will be conducted in approximately 142 adult subjects ages ≥ 18, with ≤ 8 days of symptom onset, who are SARS-CoV-2 positive as determined by a validated test. The study will enroll subjects who have at least one of the following COVID-19-related symptoms indicating mild disease: fever (temperature ≥100.4), anosmia (loss of taste or smell), cough, sore throat, gastrointestinal complaints (e.g. nausea, vomiting or diarrhea), chills, congestion or runny nose, headaches, muscle or body aches, fatigue, without shortness of breath or dyspnea (RR<20, SpO2 >93% on room air), or asymptomatic patients who have tested positive for COVID-19 via a validated test within the past 4 days. Subjects will be treated with 125 mg LAM-002A PO, BID, or with placebo PO, BID for 10 days (20 doses). The treatment schedule is outlined in the Schedule of Activities (SoA), Table 1. Subjects will be followed at 4, 6, 8, 11, 22 and 28 days after the treatment start.

Subjects will be randomized using a permuted block scheme (with variable block size) in a 1:1 ratio to one of the two groups: (1) LAM-002A, or (2) placebo. To assure at least 71 placebo participants have a viral load $\geq 2 \times 10^3$ copies/mL (the lower limit of detection of the assay) at Day 4, 142 participants with baseline viral load $>10^5$ copies/mL will be enrolled to achieve the primary objective; thus, an expected 142 subjects will be randomized (71 to receive LAM-002A and 71 to receive placebo). Because the existing longitudinal data on viral load in subjects are preliminary, this baseline viral load and number of participants randomized may be adjusted to allow for 71 placebo participants above the lower limit of detection of the assay ($\geq 2 \times 10^3$ copies/mL) at Day 4 so that a difference in viral clearance between the groups can be assessed.

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 an IND for LAM-002A (IND#148521) and the trial design and results will be subject to review by the FDA.

A designated clinical research organization (CRO) will serve as the operational coordinator of the study and will oversee conduct of the study at participating study centers. The CRO will perform activities relating to pharmacovigilance; site monitoring; data management and study reporting; and sample handling.

The study will employ an independent Data Safety Monitoring Board (DSMB) for safety and clinical efficacy and analysis of viral clearance efficacy data. AEs and serious adverse events (SAEs) 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 efficacy analyses and recommending study continuation, termination, or adaptation. An interim safety analysis of study data will be performed after the first 30 subjects (15 on LAM-002A and 15 on placebo) have completed treatment and have been followed up for 11 days post-first dose. During the analysis, study enrollment will not be halted. Recommendations from the DSMB will be used for decision of early termination, continuation, or study design adaptations.

5.3. Rationale for Study Design

The study is a randomized, placebo controlled, multi-center study in approximately 142 adults ages ≥18, randomized to LAM-002A or placebo in a 1:1 ratio. The study has been designed to provide data on the efficacy, safety, pharmacokinetics, and pharmacodynamics of LAM-002A in subjects with mild COVID-19 symptoms. After exposure with SARS-CoV-2, there is approximately a 5-day incubation period (range 1-14 days) (Guan et. Al., 2020; Li et.al., 2020; Lauer et. Al., 2020), after which most individuals (~80%) develop a mild disease. The study has been designed to treat individuals with antiviral LAM-002A early in the infection period, to reduce the viral load of SARS-CoV-2 and prevent COVID-19 progression.

In order to mitigate unanticipated safety issues in this COVID-19 population, an early interim safety analysis after 30 subjects (15 on LAM-002A and 15 on placebo) have been treated and followed for 11 days, will be performed, and reviewed by a DSMB for decision on study continuation, termination or study adaptation.

The primary outcome measure is reduction in SARS-CoV-2 viral load measured in nasopharyngeal samples at Day 4 in LAM-002A treated subjects compared to those on placebo. Exploratory outcome measures of SARS-CoV-2 viral load from saliva samples at Days 1, 4, 11, and 28 are included to further inform on the rate of viral clearance. For the primary and secondary objectives examining antiviral efficacy, the analysis will focus on the subgroup of randomized subjects with baseline viral load > 10^5 copies/mL. This subgroup was chosen because subjects in this group are predicted to have sufficient viral load at baseline for the study drug to show benefit when compared to placebo. Because the existing longitudinal data on viral load in participants are preliminary, this baseline viral load and number of participants randomized may be adjusted to allow for 71 placebo participants above the lower limit of detection of the assay (≥2228 copies/mL; see Section 10.1) at Day 4 such that a difference in viral clearance between the groups can be adequately assessed. Nasopharyngeal swabs to evaluate baseline viral load will be performed prior to randomization; however, results on viral load will not be available prior to initiation of treatment. Supportive analyses for viral load outcomes will be performed in all randomized participants.

Secondary outcome measures of hospitalization or death at Day 28, and clinical status determination using the Ordinal Scale will further inform on efficacy of the drug and provide

valuable information for Phase III trials. In addition, safety and tolerability analyses are planned as secondary outcome measures. Exploratory pharmacokinetic and pharmacodynamic outcome measures of target engagement and biomarkers (pro- and anti-inflammatory cytokine analysis) have been included to inform on the mechanism of action. Additional viral clearance measures, as determined from SARS-CoV-2 viral load in saliva samples are included as exploratory endpoints. Additional exploratory outcome measures are designed to explore resistance of SARS-CoV-2 genome variants to treatment with LAM-002A and how the subject's germline DNA may impact safety or efficacy of LAM-002A in this disease.

5.4. Justification for Dose

The dose of 125 mg BID LAM-002A (apilimod dimesylate) chosen for the COVID-19 trial 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 SARS-CoV-2 viral infection assays.

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 (eg, diabetes mellitus, chronic obstructive lung disease, cardiovascular disease). Thus, the population evaluated was highly relevant to the population to be studied in the LAM-002A COVID-19 trial.

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 (eg, 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 and did not cause cardiac or respiratory events that might worsen symptoms of COVID-19 or confound interpretation of COVID-19 manifestations.

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 [Cheson 2014]. Objective responses have been long-lasting, with durations exceeding 12 months among several subjects and are ongoing in 3 subjects who are still on therapy. 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 against several independent clinical isolates of SARS-CoV-2 in Vero E6 cells [Riva 2020; Kang 2020]. Based on these data (Table 2), the EC_{50} is between 10 and 23 nM and the EC_{90} is estimated to be between 10 and 400 nM in Vero E6 cells.

Table 2. Summary of LAM-002A In Vitro Activity Against SARS CoV-2

Reference	SARS-CoV-2 Isolate	Cell Line	EC_{50}	EC_{90}
AI Therapeutics	Hangzhou, China	Vero E6	<1.25 µM	<1.25 µM
Riva 2020	USA-WA1/2020	Vero E6	23 nM	>100 nM to <400 nM
Kang 2020	USA-WA1/2020	Vero E6	10 nM	>10 nM to <50 nM

These LAM-002 concentrations are similar to those active against B-cell non-Hodgkin lymphoma cell lines in vitro [Gayle 2017a]. 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 COVID-19 patients. Indeed, at 125 mg BID the plasma concentrations of active drug, which includes LAM-002 and its active metabolites (STA-5908, STA-5944, and STA-6048) weighted by their relative cell based activity and exposure, exceed the average in vitro anti-viral EC_{90} (205 nM) in Vero E6 cells by 1.5 times at trough and by 7.4 times at C_{max}. Furthermore, a rat distribution study of oral administration of [^{14}C]-apilimod suggests that lung exposures are 1.1 to 1.5 times higher than in blood, providing further rationale that 125 mg BID would provide sufficient drug levels for anti-viral activity in lung tissues.

Consequently, it is the AI Therapeutics position that the LAM-002A dosing regimen of 125 mg BID maximizes the potential for antiviral benefit in patients with COVID-19 and will be safe and well tolerated over the planned treatment course.

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. Reference is made to the National Early Warning Score (NEWS) for grading of illness intensity and the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 for severity of adverse events.

6.1. Inclusion Criteria

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

1. Men and women of age ≥18 years.
2. Written documentation of SARS-CoV-2 infection confirmed by a validated test.
3. Presence of ≥1 of the following COVID 19-related symptoms indicating mild disease: fever (temperature ≥100.4), anosmia (loss of taste or smell), cough, sore throat, gastrointestinal complaints (e.g. nausea, vomiting or diarrhea), chills, congestion or runny nose, headaches, muscle or body aches, fatigue, or asymptomatic patients who have tested positive for COVID-19 via a validated test within the past 4 days.
4. If symptomatic, symptom onset ≤8 days.
5. For female subjects of childbearing potential, a negative urine (or serum) pregnancy test.
6. For female subjects of childbearing potential, willingness to use a protocol-recommended method of contraception from the start of the screening period until ≥30 days after the final dose of study therapy. *Note: 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 serum or urine beta human chorionic gonadotropin [βHCG]); or is menopausal (age ≥50 years with amenorrhea for ≥6 months).*
7. For male subjects who can father a child and are having intercourse with females of childbearing potential who are not using adequate contraception, willingness to use a protocol-recommended method of contraception from the start of study therapy until ≥30 days after the final dose of 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. *Note: A male subject is considered able to father a child unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy.*
8. Willingness and ability of the subject to ingest study drug capsules.
9. Willingness of the subject to comply with scheduled visits, drug administration plan, protocol-specified laboratory tests, study procedures, and study restrictions.

10. Evidence of a personally signed informed consent indicating that the subject is aware of the nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential risks and discomforts, potential benefits, and other pertinent aspects of study participation.

6.2. Exclusion Criteria

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

1. Respiratory rate ≥20 breaths per minute.
2. Oxygen saturation by pulse oximetry ≤93% on room air or requirement for supplemental oxygen to maintain oxygen saturation >93%.
3. Total NEWS score ≥6 or presence of a score of 3 on any of the individual NEWS parameters.
4. Radiographic evidence of pulmonary infiltrates (clinical X-ray within 2 days of referral)
5. Hepatic profile showing any of the following:
   - Serum alanine aminotransferase (ALT) >5 × upper limit of normal (ULN) (CTCAE Grade ≥3).
   - Serum aspartate aminotransferase (AST) >5 × ULN (CTCAE Grade ≥3).
   - Serum bilirubin >1.5 × ULN (CTCAE Grade ≥2).
6. 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).
7. Presence of a cancer with disease manifestations or therapy that could adversely affect subject safety or longevity, create the potential for drug-drug interactions, or compromise the interpretation of study results.
8. Significant cardiovascular disease (e.g. myocardial infarction, arterial thromboembolism, cerebrovascular thromboembolism) within 1 month prior to start of study therapy; unstable angina; symptomatic peripheral vascular disease; CTCAE Grade ≥2 congestive heart failure; or uncontrolled CTCAE Grade ≥3 hypertension (diastolic blood pressure ≥100 mmHg or systolic blood pressure ≥160 mmHg) despite antihypertensive therapy.
9. Significant screening ECG abnormalities, including atrial fibrillation/flutter, 2nd degree atrioventricular (AV) block type II, 3rd-degree AV block, Grade ≥2 bradycardia, or corrected QT (QTc by Fridericia [QTcF]) >480 msec (Grade >1).
10. Gastrointestinal disease (e.g. gastric or intestinal bypass surgery, 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.
11. Pregnancy or breastfeeding.
12. Prior solid organ transplantation.
13. Use within 5 days prior to randomization of an approved or investigational therapy intended to treat COVID-19 (e.g. remdesivir, anti-interleukin [IL]-6 antibodies, therapeutic anti-SARS-COV-2 antibodies or post-convalescent plasma, anti-SARS-COV-2 vaccine, Bruton

tyrosine kinase [BTK] inhibitor), use within 3 months of chloroquine or hydroxychloroquine. *Note: Subjects are not precluded from undergoing evaluations involving observation, noninvasive diagnostic procedures or sampling, or questionnaires as follow-up to a prior study or as components of a concurrent noninterventional study*.

14. Use within 5 days prior to randomization 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).
15. Use within 5 days prior to randomization 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.
16. Use within 5 days prior to randomization of a drug known to prolong the QT interval (see Appendix 15.2 for a list of drugs that are considered to have a known propensity to prolong the QT interval).
17. Ongoing immunosuppressive therapy including systemic or enteric corticosteroids. (Note: At study entry, subjects may be using intraarticular, inhaled, or topical corticosteroids. During study therapy, subjects may use systemic, enteric, intraarticular, inhaled, or topical corticosteroids as required for intercurrent conditions.)
18. Any illness, medical condition, organ system dysfunction, or social situation, including mental illness or substance abuse, deemed by the investigator to be likely to interfere with a subject's ability to provide informed consent, adversely affect the subject's ability to cooperate and participate in the study, or compromise the interpretation of study results.

7. STUDY DRUG ALLOCATION

7.1. Randomization

After a subject has completed the necessary screening assessments and has been confirmed to be eligible, the subject can be randomized into the study. In order to obtain a treatment arm assignment for a subject, a site representative will submit the appropriate information for randomization, and the system will make an assignment of a study drug bottle number. Subjects will be randomized in a 1:1 ratio (Arm A:Arm B) to either of the following treatment assignments:

- Arm A: LAM-002A
- Arm B: Placebo

In order to balance treatment allocation, a permuted block centralized randomization will allocate subjects.

It is anticipated that subjects will usually begin study drug immediately after randomization Day 1 of the study. In case of administrative delays, every attempt should be made to initiate study drug treatment by Day 2.

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 (see Section 8.3) 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.

8. STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT

8.1. Blinded 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 formulated in capsules with identical appearance to the capsules containing active drug. The inactive component in placebo capsules is microcrystalline cellulose.

8.1.2. Source

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

8.1.3. Packaging and Labelling

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 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.

Study centers will be provided with initial and updated product stability data, when available.

8.1.5. Dispensing

A pharmacist or other qualified staff member will dispense bottles containing study drug (LAM-002A or 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

After the completion of the treatment course, empty, partially used, or full bottles of study drug (LAM-002A or placebo) will 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, the subject's dosing diary should be reviewed, any incomplete or inconsistent entries should be addressed, and the dosing diary should be copied. 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 or 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 randomized in a 1:1 ratio to receive study therapy, comprising either LAM-002A, 125 mg (five 25-mg capsules/dose) orally BID or placebo (five capsules/dose) orally BID for 10 days.

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).

On Day 1, subjects should take the drug 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 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. 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

On Day 1, subjects should ingest the study drug (LAM-002A or placebo) while fasting (defined as no food with the exception of clear liquids for ≥2 hours before and ≥1 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.

Of note, the first (on-site) dose might occur at a time in the afternoon that would mean that the next scheduled (at home) dose is after midnight. In such a subject, the second dose may be taken in the morning of Day 2. Subsequent doses may then be adjusted to reflect 12-hour intervals following the time of administration of this second dose. For example, if the second dose is taken at 8AM, subsequent doses should follow an 8AM-8PM dosing schedule.

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. 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, 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, 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. 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).

8.4. Supportive Care

8.4.1. 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.

8.4.2. Antibiotics, Antifungals, and Antivirals

Local practices or guidelines regarding infection prophylaxis may be followed. Subjects developing an intercurrent infection other than with SARS-CoV-2 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 8.4.9 and Section 15.1. Continuation of study therapy during treatment for an intercurrent infection is at the discretion of the investigator.

8.4.3. Anti-SARS-CoV-2 Therapies

At baseline and during study participation, study subjects may not receive chloroquine, hydroxychloroquine, BTK inhibitors, anti-SARS-CoV-2 vaccines, or other investigational anti-SARS-CoV-2 drugs as long as they remain investigational. Subjects may not be receiving remdesivir, anti-IL-6 antibodies, therapeutic anti-SARS-CoV-2 antibodies, or post-convalescent plasma at baseline but may have such drug introduced as appropriate if they develop respiratory failure, cardiac failure, or other serious manifestations of COVID-19. Continued study therapy together with these additional therapies is permitted at the discretion of the investigator. Subjects are not allowed to participate concurrently in any other therapeutic clinical study.

8.4.4. Anticoagulants

Use of local anticoagulation or antithrombotic agents to maintain a venous access catheter is permitted. In addition, subjects who develop conditions that require anticoagulant therapy are permitted to receive such drugs and are not required to discontinue study participation.

8.4.5. 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.

8.4.6. 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.

8.4.7. Antihistamine, Antiinflammatory, or Antipyretic, Drugs

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

8.4.8. Corticosteroids

At study entry, subjects may be using systemic, intraarticular, inhaled, or topical corticosteroids. During study therapy, subjects may use systemic, intraarticular, enteric, inhaled, or topical corticosteroids as required for intercurrent conditions.

8.4.9. 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.

8.4.10. 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. Drugs that are known to prolong QT Interval or cause Torsades De Pointes are listed in Section 15.2.

8.4.11. Hematopoietic Support

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

8.4.12. Cardiopulmonary Support

Study subjects should not be requiring supplemental oxygen or other cardiopulmonary support at baseline. Subjects may be offered any medically necessary cardiopulmonary support during study participation. Study drug (LAM-002A or placebo) may be continued at investigator discretion as long as the subject is able to be administered the study drug via the enteral route.

8.5. Study Restrictions

8.5.1. 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.

8.5.2. 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 serum or 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 (ie, 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.

8.5.3. 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.

8.6. Duration of Study Drug Administration and Study Participation

Subjects may receive study therapy (LAM-002A or placebo) for as long as 10 days. However, the occurrence of any of the following events requires treatment 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
- Pregnancy or breastfeeding
- 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

Subjects who discontinue study therapy will continue on study for acquisition of safety information through at least Day 28. Study follow-up will continue through Day 28 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. Worsening manifestations of the underlying infection (e.g. increase in COVID-19 manifestations) may be considered AEs in this study.
- 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 9.7.2 for additional information).

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 (ie, all deaths occurring between signing of the consent form to within 30 days after last study drug administration), including deaths due to COVID-19 if no other event more satisfactorily explains the reason for death. Deaths that occur as a result of an AE that started during the study period should be reported. Death is not an SAE term; the reported AE should be the event that caused the death. Death is the outcome of this SAE.
- Life-threatening situation (ie, 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 the cancer, logistical issues (e.g. lengthy travel), or the convenience of the subject or clinical personnel are not considered serious.
- Persistent or significant disability/incapacity.
- Congenital anomaly/birth defect in the offspring of a subject who received the investigational medicinal product.
- 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 Day 28 of the study.

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 (ie, 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 9.4)
- A description of the relatedness of the AE to the study drug or to a study procedure (see Section 9.5)
- The action taken due to the AE
- The outcome of the AE

9.4. Grading of the Severity of an Adverse Event

The severity of AEs will be graded and reported using the CTCAE, Version 5.0.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 3.

Table 3. 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).

9.5. 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 4.

It should be emphasized that the determination of the relationship of an adverse event to study drug (LAM-002A or placebo) should be based on the presumption that the study subject is receiving active LAM-002A even though the blind remains unbroken. As noted in Section 8.3, unblinding should be avoided unless absolutely necessary for a subject's well-being; breaking the blind should not be performed merely to obtain enhanced certainty regarding the relationship of an adverse event to study drug.

Table 4. 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.

9.6. 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 Day 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 Day 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 9.7.2).

9.7. Study Center Reporting Requirements

9.7.1. Adverse Event Reporting Requirements

Classification of an event as serious or nonserious (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 5.

Table 5. Study Center Reporting Requirements for Adverse Events

Classification	Reporting Time	Reporting Action
Serious	Within 24 hours of becoming aware of the event	E-mail report on designated SAE report form to the sponsor or designee [a] and to the study center IRB, as per local IRB/IEC requirements
	Within 10 working days	E-mail copies of relevant source documents (e.g. progress notes, laboratory and diagnostic test results, discharge summaries) [b] to the sponsor or designee [a].
	Per eCRF submission procedure	Record and submit information on appropriate eCRFs.
Nonserious	Per eCRF submission procedure	Record and submit information on appropriate eCRFs.

a. See contact information provided.
b. Subject name, address, and other personal identifiers should be obscured but without losing the traceability of a document to the study subject identifiers.

Abbreviations: eCRF=case report form; IRB/IEC= institutional review board/independent ethics committee; SAE=serious adverse event

For SAEs, in addition to completing the AE portion of the eCRF, an SAE report form must also be completed and emailed within 24 hours of first awareness of the event to the sponsor (or designee).

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) should also be provided. 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.

9.7.2. Pregnancy

Each female subject should be instructed to inform the investigator immediately if she becomes pregnant at any time between the start of study screening until 30 days after the last administration of study drug. Similarly, a male subject should also be instructed to inform the investigator immediately if his female partner becomes pregnant during the 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 pregnancy report forms. However, if the outcome of the pregnancy meets the criteria for classification as an SAE (ie, spontaneous abortion, induced abortion due to complications, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator should follow the procedures for reporting SAEs (ie, report the event to the sponsor [or designee] and follow up by submission of the appropriate AE eCRFs (see Section 9.7.1).

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 (ie, there is no required minimum follow-up of a presumably normal infant before the pregnancy outcome report eCRF 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 pregnancy report form and forwarded to the sponsor (or designee) for contact list) 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 30 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).

9.7.3. Contact Information for Reporting an SAE or Pregnancy

Contact information for reporting an SAE or Pregnancy will be managed by the CRO.

9.8. 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 9.5). 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, fax, or overnight 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 6.

General safety laboratory assays (serum pregnancy test, serum chemistry, hematology,) will be performed using standard clinical pathology methods 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.

Viral load measurements from nasopharyngeal swabs at Days 1, and 4 will be conducted at Covance using the Quantification of COVID-19 Viral Load using the 2019-nCoV Real-Time RT-PCR Viral Load assay on Applied Biosystems QuantStudio 7/12K Flex Real-Time PCR system (v2) assay. The method has been validated to CAP/CLIA standards by Covance. The quantitative assay does not have EUA, but the non-qualitative version of the assay developed by Covance does have EUA. The limit of detection of the assay is set to the lower limit of quantification (LLOQ) of the quantitative 2019-nCoV CDC EUA assay using respiratory specimens which was determined using a synthetic RNA panel prepared at different target input levels at the lower end of the AMR. The panel was tested 5 times in triplicate in at least one run.

The LLOQ for 2019-nCoV CDC EUA assay for respiratory swabs is 3.348 Log10 copies/mL (2228 copies/mL). For values below the LLOQ that are still detected, a value of "detected" will be reported. When no virus is detected a value of "undetected" will be reported.

The method for saliva samples is currently completing similar CAP/CLIA validation at Covance. Details for both methods will be included in the Laboratory Manual.

Pharmacodynamic and biomarker assessments will be conducted at contract laboratories designated by the sponsor.

Clinical assessments (body weight and height, vital signs, oxygen saturation) 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 6. Laboratory and Other Parameters to Be Assessed

Test/Procedure	Parameters
Laboratory – Safety	
Urine (or serum) pregnancy test	Urine or serum 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.
Hematology	Hematocrit, hemoglobin, erythrocyte count, absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils Platelet count
Laboratory – Pharmacokinetic[1]	
Plasma pharmacokinetics	Plasma LAM-002A 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 for potential metabolite analyses
Laboratory – Pharmacodynamic[1]	
Peripheral blood and nasopharyngeal swabs for cellular pharmacodynamics	Plasma cytokines might be analyzed for levels of IL-12, IL-23, IL-6, IFN-γ, IL-10 and GM-CSF (additional cytokines may be analyzed in parallel)
	Target engagement biomarkers might be assessed via RNA-seq or qRT-PCR from RNA isolated from nasopharyngeal swabs and PBMC, or in plasma via established Luminex and or ELISA assays
Laboratory – Disease-related	
SARS-CoV-2 assessments	Nasopharyngeal swab and saliva to determine SARS-COV-2 viral load using a qRT-PCR method.
SARS-CoV-2 mutational analysis	Mutational profiling of SARS-CoV-2 viral genome might be analyzed by RNA-seq or comparable technology[1]
Genetic Polymorphism in COVID-19 subjects	Analysis of germline DNA sequence polymorphisms in genomic DNA isolated from blood or Nasopharyngeal swabs[1]
Other	
Body weight/height	Weight in kilograms, height in centimeters
Body temperature	Temperature in degrees Celsius
Blood pressure	Diastolic and systolic blood pressure in mm Hg
Oxygen saturation	% saturation
12-lead ECG	Heart rate, cardiac intervals, wave form abnormalities, ectopy

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CK=creatine kinase, DNA=deoxyribonucleic acid, ECG=electrocardiogram, LDH=lactate dehydrogenase, PCR=polymerase chain reaction, RNA=ribonucleic acid.
[1]Samples will be collected for pharmacokinetic, immunogenicity, and genetic exploratory end points. The analysis for these exploratory endpoints is optional

10.2. Sample Shipping, Storage, and Retention

Routine clinical safety samples (for pregnancy test, serum chemistry, and hematology) will be analyzed at the clinical laboratory at the study center and will not be shipped. These samples will not be stored and will be discarded promptly after analysis.

Other samples (viral nasopharyngeal swab samples; saliva; plasma for pharmacokinetics; blood and plasma for pharmacodynamics) will be prepared 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.

11. EFFICACY ASSESSMENTS

11.1. Primary Efficacy Endpoint: Viral Clearance at Day 4

The primary efficacy outcome measure evaluates SARS-CoV-2 viral load at Day 4 for LAM-002A or placebo-treated subjects. SARS-CoV-2 viral load will be measured in nasopharyngeal specimens by a qRT-PCR method. Analysis will focus on $\log_{10}$ viral load on Day 4 adjusted for baseline viral load at Day 1 in subjects with baseline viral load $>10^5$ copies/mL.

11.2. Secondary Efficacy Endpoint

11.2.1. Clinical Efficacy

An additional secondary efficacy endpoint measures the proportion of subjects treated with LAM-002A who progressed to hospitalization or who died at Day 28 of randomization compared to those in the placebo arm.

The need for referral for consideration for hospitalization will be assessed based on the CDC guidelines for presentation of mild/moderate, severe, and critical disease

- **Mild to moderate**: mild symptoms (fever [temperature ≥100.4], cough, sore throat, anosmia, malaise, headache, or muscle pain, gastrointestinal symptoms) up to mild pneumonia
- **Severe:** dyspnea, hypoxia, or >50% lung involvement on imaging
- **Critical:** respiratory failure, shock, or multiorgan system dysfunction

Severe and critical disease require hospitalization.

The National Early Warning Score (NEWS) has demonstrated an ability to discriminate patients who are at risk of poor outcomes (Smith et.al., 2015), and has been recommended by the World Health Organization (WHO, 2020). This score is based on 7 clinical parameters. The vital sign scores as measured by the NEWS (Table 1) provides measures of dyspnea, hypoxia as well as other vital signs important to COVID-19 symptoms such as temperature and blood pressure.

Vital signs related to COVID-19 illness will be monitored as specified in Table 7. A composite score of vital sign parameters is calculated at baseline and at each visit. Change of NEWS from baseline will be used to assess resolution or progression of disease and decision for hospitalization.

The following criteria will be used to determine need for hospitalization:

- A composite NEWS >6, or
- One NEWS parameter score of 3 (e.g. RR≥25, Oxygen saturation <91), or
- Respiratory failure, or
- Severe presentations of other COVID-19 symptoms, or
- ECOG Status (see table in Section 15.3)

If the NEWS score increases during the follow-up visits, the subject will be followed more closely with subsequent day tele-health visits until the NEWS score improves or subject further declines, requiring hospitalization.

Table 7 National Early Warning Score (NEWS)

PHYSIOLOGICAL PARAMETERS	3	2	1	0	1	2	3
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturations	≤91	92 - 93	94 - 95	≥96			
Any Supplemental Oxygen		Yes		No			
Temperature	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	
Systolic BP	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart Rate	≤40		41 - 50	51 - 90	91 - 110	111 - 130	≥131
Level of Consciousness				A			V, P, or U

Level of consciousness = alert (A), and arousable only to voice (V) or pain (P), and unresponsive (U).

NEWS Composite Score

NEWS = 0-4 Low score: Assessment by a competent registered nurse who should decide if a change to frequency of clinical monitoring or an escalation of clinical care is required.

NEWS = 5-7 Medium Score: Urgent review by a clinician skilled with competencies in the assessment of acute illness.

NEWS ≥ 7 High Score: Emergency assessment by a clinical/critical care outreach team with critical-care competencies and usually transfer of the patient to a higher dependency care area.

11.2.2. Hospitalization: Clinical Status

The secondary efficacy endpoint evaluates COVID-19 clinical status including subjects who become hospitalized and continue LAM-002A/placebo treatment. Clinical status is defined by the ordinal scale. For subjects (who have the same ordinal score), control versus experimental arms will be compared based on percentage of subjects at each score on Day 28.

COVID-19 Severity Ordinal Scale scores in LAM-002A-treated and placebo-treated subjects will be determined at Day 28 based on the following scores:

1. Not in the hospital
2. Hospitalized, requiring low flow supplemental oxygen (such as nasal cannula)
3. Hospitalized, not on invasive ventilation (such as 100% non-rebreather, BIPAP), (pre-ICU)
4. Hospitalized, in the ICU, on invasive ventilation or ECMO
5. Dead

12. STATISTICAL CONSIDERATIONS

This is a double-blind placebo-controlled trial to determine the superiority of LAM-002A compared to placebo in reducing viral load during a 10-day course of therapy.

COVID-19 patients that fulfill all enrollment criteria and provide informed consent to study participation will have their baseline assessments performed and will be randomized using a permuted block scheme (with variable block size) in a 1:1 ratio to one of the two groups: (1) LAM-002A, or (2) placebo.

The study will include an early evaluation of safety, and an interim analysis. Full details of the statistical methods will be developed and outlined in the statistical analysis plan (SAP) and filed with the study sponsor prior to database lock.

12.1. Statistical Hypotheses

All tests performed will be tests of superiority.

For the primary efficacy endpoint, the hypothesis that LAM-002A results in a reduction in viral load compared to placebo in the subgroup of participants with baseline nasopharyngeal viral load $> 10^5$ copies/mL will be tested.

12.2. Sample Size Determination

The study is designed to have high power at a moderate significance level to detect a signal of benefit for the viral load outcome. The sample size calculation is based on the primary endpoint of interest: $\log_{10}$ respiratory (nasopharyngeal swab) viral load at Day 4 post-randomization.

Given the limited data on the variability of the change in $\log_{10}$ viral load, the study is powered based on detecting a moderate standardized effect size of 0.3 using an analysis of covariance (ANCOVA), adjusting for baseline $\log_{10}$ viral load. (NOTE: For ANCOVA, the effect size is the standard deviation of the treatment means divided by the pooled standard deviations of the observations. An ANCOVA standardized effect size of 0.3 is equivalent to a Cohen's d of 0.60). To be conservative, a R-squared of 0 between the $\log_{10}$ viral RNA at 4-days and baseline $\log_{10}$ viral RNA was assumed. With a power of 90%, and a type I error rate of 20% (2-sided), it will be possible to detect the hypothesized 0.3 standardized effect size with 74 total patients – 37 patients per group with a 1:1 randomization. We will enroll a sample size of 142 to assure that a sufficient number of participants with baseline viral load $>10^5$ copies/ml. The table below shows the power to detect an effect size of 0.3 given 10% loss to follow-up and various proportions enrolled with baseline viral load $>10^5$ copies ml.

	Proportion of Enrolled Participants with $>10^5$ copies/ml						
	0.40	**0.50**	**0.60**	**0.70**	**0.80**	**0.90**	**1.00**
Power to Detect Effect Size of 0.3	0.79	0.86	0.91	0.94	0.96	0.97	0.98

Based on available data regarding the distribution of viral load, it is conservatively estimated that ≥50% of randomized participants will have a baseline viral load $>10^5$ copies/mL. The table above demonstrates that enrolling 142 will provide sufficient power even if the proportion with baseline viral load $>10^5$ copies/ml is as low as 40%. The prevalence of this subgroup will be monitored and adjustments to overall sample size may be made if necessary.

12.3. Analysis Sets

12.3.1. Intention to Treat (ITT) Population

The intention-to-treat (ITT) population includes all participants randomized according to their initial randomized assignment regardless of the treatment actually received.

12.3.2. Antiviral Efficacy Analysis Population

The antiviral efficacy analysis population will consist of all randomized participants with a baseline viral load $>10^5$ copies/mL.

12.3.3. Per Protocol (PP) Population

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

12.3.4. Safety Population

The safety population will include all randomized subjects who received at least one dose of the study drug.

12.4. Statistical Analyses

12.4.1. General Considerations

This is a double-blind placebo controlled randomized trial testing the superiority of LAM-002A compared to placebo for Day 4 viral load at the two-sided overall type I error rate of 0.20. Secondary hypotheses will be described according to the appropriate summary statistics (e.g., proportions for categorical data, means with 95% confidence intervals for continuous data, median for time-to-event data). Diagnostic tests and sensitivity analyses will be performed. Parametric distributional assumptions will be checked. If assumptions fail, other distributions will be considered prior to transformations and non-parametric methods for sensitivity analysis. A statistical analysis plan (SAP) will be developed and filed with the study sponsor prior to database lock.

12.4.2. Comparability of Baseline Characteristics.

Distributions of baseline demographic and clinical characteristics will be summarized by intervention group. Comparability for continuous variables will be examined graphically and by summary statistics (means, medians, quartiles, etc.). Categorical variables will be examined by calculating frequency distributions. No inferential statistics will be calculated.

12.4.3. Analysis of Primary Outcome: Viral Load in Nasopharyngeal Samples at Day 4

The primary analysis will test whether the viral load in nasopharyngeal samples is lower at Day 4 in those receiving LAM-002A compared to placebo. All participants in the antiviral efficacy analysis set (i.e. the subgroup with baseline viral load $>10^5$ copies/mL) will be included in the primary analysis. Viral load will be measured by a qRT-PCR test at Days 1 and 4. The analysis for the primary endpoint will focus on the $\log_{10}$ viral RNA on Day 4. A repeated measures mixed model will be used to compare the two treatment groups. The mixed model will jointly model day 1 and day 4 viral load and will allow for the inclusion of all participants with at least one viral load assessment [Carpenter 2007]. The model will include fixed effects for treatment and age. Random effects will be included for subject and site. Linear contrasts will be used to compare the difference between groups for Day 4. This difference will be conditional on baseline viral load and is equivalent to an analysis adjusted for baseline [Carpenter 2007]. 95% CIs will be estimated for treatment differences at Day 4. A supportive analysis will be conducted using the ITT population, stratified by baseline viral load $>10^5$ copies/mL vs. viral load $\leq 10^5$ copies/mL.

12.4.4. Analysis of Secondary Outcomes

The statistical and analytical methods that will be used to evaluate the secondary endpoints are described in this section.

12.4.4.1. Secondary Outcome: Hospitalization or Death Within 28 Days

The proportion of those progressing to hospitalization or death within 28 days of randomization will be compared between treatment groups using logistic regression (Ge 2011). All participants in the ITT population will be included in this analysis. Covariates in the analysis will include age. Site will be included as a random effect. The risk difference and 95% confidence interval will be estimated. Supportive analysis of this outcome will use the antiviral efficacy analysis population and the PP population.

12.4.4.2. Clinical Status (Disease Progression)

The distribution of ordinal scale severity results will be summarized by treatment arm as percentages in the ITT population. A proportional odds model will be used to compare groups on this ordinal scale. The common odds ratio measures the effect size and is valid under the proportional odds assumption that will be verified via a goodness of fit likelihood ratio test. The model will include fixed effects for treatment, and age. Hypothesis tests for the model are nearly identical to the Wilcoxon Rank Sum test. Supportive analysis of this outcome will use the antiviral efficacy analysis population and the PP population.

12.4.4.3. Secondary Outcome: Oxygen Saturation (O2 sat)

A logistic regression using generalized estimating equations will be used compare the proportion of subjects at or above 95% oxygen saturation (O2 sat) between LAM-002A versus placebo as measured on Days 1, 4 and 11 in participants in the ITT population. Individuals requiring respiratory assistance, hospitalized or who died will be considered as having O2 sat <93%. Those who require baseline O2 will be excluded from the analysis. Supportive analysis of this outcome will use the antiviral efficacy analysis population and the PP population.

12.4.5. Exploratory Endpoints

Analysis for exploratory endpoints will be defined in the study SAP or separate reports, as appropriate.

12.4.6. Subgroup Analyses

Heterogeneity of treatment effect (HTE) for the primary and secondary progression to hospitalization or death outcome will be examined for the following subgroup variables: days from onset of symptoms to randomization, NEWS score at randomization and sex (male vs. female). HTE will be evaluated within a mixed model for the primary outcome and a logistic regression for the secondary progression outcome. The models will include treatment, site, the subgroup variable, and the interaction of the subgroup variable with time. Differences in means or risk with 95% confidence intervals will be estimated for the treatment difference within each level of the subgroup variable. The significance test of the interaction will be used to formally test HTE at the two-sided 0.05 significance level.

12.4.7. Plan for Missing Data

Several strategies will be imposed to minimize the impact of missing data on conclusions. Prevention is the most obvious and effective manner to control bias and loss of power from missing data (NRC 2010). This protocol will follow the intent to treat principle, requiring follow-up of all subjects randomized regardless of the actual treatment received (Lachin, 2000). The only reasons for not considering a subject in analyses will be withdrawal of consent, a false positive test for SARS-CoV-2, or lost to follow-up. The informed consent and protocol will distinguish between treatment discontinuation and study withdrawal and the consent will also include a statement about the importance of continuing data collection despite treatment discontinuation. Alternative contact information will be identified on entry into the study to minimize loss-to follow-up. Timely data entry combined with weekly missing data reports will trigger protocols for tracking and obtaining missing data items or outcome assessments. Despite these prevention efforts it is reasonable to assume missing data will occur. The primary analysis is valid under the assumption that missing data is missing at random (MAR). The plausibility of this assumption will be evaluated by determining the extent of missing data and using logistic regression to identify factors associated with dropout. While differential rates of dropout between groups or high loss to follow-up are not expected, sensitivity analysis using pattern-mixture and selection models under missing not at random (MNAR) assumptions will be performed to examine the robustness of conclusions of the primary analysis to missing data.

12.4.8. Safety and Tolerability Analyses

Adverse events (AEs) and serious adverse events (SAEs) will be categorized by severity and relation to study drug using the Safety population. AEs will be classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Safety endpoints including SAEs, Grade 3 and 4 adverse events and signs compatible with cardiac arrhythmias, allergic reactions, gastrointestinal, hepatobiliary, eye and ear, blood and lymphatic system disorders and acute exacerbation of lung disorders will be described by treatment group. Each AE will be counted once for a given participant and graded by severity and relationship to COVID-19 or study intervention. AEs will be presented by system organ

class, duration (in days), start- and stop-date. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs will be presented in tables and listings.

Differences between treatment groups for safety outcomes will be tested at the 0.05 (2-sided level of significance) without correction for multiple testing.

12.4.8.1. Adverse Events

Treatment-emergent AEs and non-TEAEs (those occurring prior to administration of study medication or that first occurred prior to study drug administration and did not worsen in frequency or severity) will be listed. TEAEs will be defined as AEs that occur on or after the date and time of study drug administration, or those that first occur pre-dose but worsen in frequency or severity after study drug administration. AEs will be followed-up until complete resolution, or until the PI or Sub-Investigator judges safe to discontinue follow-up.

The incidence of TEAEs will be summarized using the safety population. The MedDRA® dictionary Version 23 will be used to classify all AEs reported during the study by system organ class (SOC) and preferred term (PT). Incidence of subjects who experienced TEAEs will be presented by treatment and overall, SOC, PT, by Investigator-assessed relationship and also by severity. Each subject may only contribute once to each of the incidence rates, for a TEAE following a given treatment, regardless of the number of occurrences; the highest severity or highest relationship will be presented, as appropriate. In each table, SOC will be presented in descending order of overall incidence rate in terms of frequency of subjects and then in frequency of events (alphabetical order will be used in case of equal rates). For each SOC, PT will be presented the same way.

Incidence of TEAEs (number of events) will also be presented by treatment and overall, by SOC, and PT, by Investigator-assessed relationship and severity.

Severity of AEs will be rated according to CTCAE criteria as outlined in Section 9.4 and defined in Table 3 as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening) and Grade 5 (fatal).

12.4.8.2. Laboratory Parameters

Clinical laboratory tests including biochemistry, hematology, and other screening tests, will be performed as listed in Table 6, and at time points specified in the SoA (Table 1). 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 “N” (Normal Range) for categorical parameters.

Descriptive statistics (mean, median, SD, Min, Max, and sample size) for each clinical laboratory test (continuous variables) will be presented. Change from baseline to study exit will also be presented. For a given laboratory test, any value (scheduled or unscheduled), prior to the first dosing will replace any missing screening value (if scheduled value is missing). However, unscheduled results will not be included in the summary tables. For categorical variable, the number of subjects (frequency and percentage) will be tabulated by results (e.g., negative, positive, trace, etc.). A summary table of shifts from screening 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.

12.4.9. Other Safety Analyses

Any other safety analysis will be made on the safety population.

12.5. Interim Analyses

The study will incorporate an interim analysis for safety after the first 30 subjects (15 on LAM-002A and 15 on placebo) have completed treatment and have been followed up to Day 11. Recommendations from an independent Data Safety Monitoring Board (DSMB) will be used for decision of early termination or design adaptations (see table of Death Trigger Study Termination below). No formal assessment of futility or efficacy will be performed at this first interim report.

Subsequent interim DSMB reports will be reviewed with no more than 6 months between reviews. In addition to safety, at 50% enrollment the DSMB will review the proportion of participants that have a baseline viral load of $>10^5$ copies/ml. Based on this proportion the DSMB may recommend an increase in sample size to assure a sufficient number of participants in the subgroup for primary analysis. If a recommendation for a sample size increase is being considered, futility will be examined via conditional power to assist in this determination. Details will be provided in the SAP.

The first interim analysis for safety will be conducted and presented to the DSMB when 15 participants in each treatment arm have reached 11 days following randomization. At this review, it is proposed that the study be stopped if mortality is significantly higher in the LAM-002A arm compared to placebo arm based on a Fisher's exact test. Table 8 shows the differences in deaths between the LAM-002A and placebo arm that will prompt discontinuation of the study.

Table 8. Death Boundary for Study Termination

Placebo Deaths, n	LAM-002A Deaths, n	Difference (LAM-002A – Placebo)	Fisher's Exact P-Value
0	5	5	0.042
1	7	6	0.035
2	8	6	0.05
3	10	7	0.025
4	11	7	0.027
5	12	7	0.025
6	13	7	0.021
7	13	6	0.050

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 and 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 and 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 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 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 to ensure compliance with the protocol and the 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 9.8).

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

Reference: [FDA 2020]
Abbreviation: CYP=cytochrome P450 enzyme

15.2. Drugs Known to Prolong the QT Interval and/or Cause Torsades De Pointes

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Amiodarone	Cordarone®, Pacerone®, Nexterone®	Antiarrhythmic	Abnormal heart rhythm
Anagrelide	Agrylin®, Xagrid®	Phosphodiesterase 3 inhibitor	Thrombocythemia
Arsenic trioxide	Trisenox®	Anticancer	Cancer (leukemia)
Astemizole (removed from market)	Hismanal®	Antihistamine	Allergic rhinitis
Azithromycin	Zithromax®, Zmax®	Antibiotic	Bacterial infection
Bepridil (removed from market)	Vascor®	Antianginal	Angina Pectoris (heart pain)
Chloroquine	Aralen®	Antimalarial	Malaria
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	Antipsychotic / Antiemetic	Schizophrenia, nausea, many others
Cilostazol	Pletal®	Phosphodiesterase 3 inhibitor	Intermittent claudication
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®	Antibiotic	Bacterial infection
Cisapride (removed from market)	Propulsid®	Gastrointestinal stimulant	Increase gastrointestinal motility
Citalopram	Celexa®, Cipramil®	Antidepressant, selective serotonin reuptake inhibitor	Depression
Clarithromycin	Biaxin®, Prevpac®	Antibiotic	Bacterial infection
Cocaine	Cocaine	Local anesthetic	Anesthesia (topical)
Disopyramide	Norpace®	Antiarrhythmic	Abnormal heart rhythm
Dofetilide	Tikosyn®	Antiarrhythmic	Abnormal heart rhythm
Domperidone (only on non-US market)	Motilium®, Motillium®, Motinorm Costi®, Nomit®	Antinausea	Nausea, vomiting
Donepezil	Aricept®	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)
Dronedarone	Multaq®	Antiarrhythmic	Abnormal heart rhythm
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®	Antipsychotic / Antiemetic	Anesthesia (adjunct), nausea
Erythromycin	E.E.S.®, Robimycin®, Emycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Zineryt®, Abboticin®, Abboticin-ES®, Erycin®, PCE Dispertab®, Stiemycine®, Acnasol®, Tiloryth®	Antibiotic	Bacterial infection, increase gastrointestinal motility

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Escitalopram	Cipralex®, Lexapro®, Nexito®, Anxiset-E® (India), Exodus® (Brazil), Esto® (Israel), Seroplex®, Elicea®, Lexamil®, Lexam®, Entact® (Greece), Losita® (Bangladesh), Reposil® (Chile), Animaxen® (Colombia), Esitalo® (Australia), Lexamil® (South Africa)	Antidepressant, selective serotonin reuptake inhibitor	Depression (major), anxiety disorders
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®	Antiarrhythmic	Abnormal heart rhythm
Fluconazole	Diflucan®, Trican®	Antifungal	Fungal infection
Gatifloxacin (removed from market)	Tequin®	Antibiotic	Bacterial infection
Grepafloxacin	Raxar®	Antibiotic	Bacterial infection
Halofantrine	Halfan®	Antimalarial	Malaria
Haloperidol	Haldol® (US & UK), Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol® (Germany), Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®	Antipsychotic	Schizophrenia, agitation
Ibogaine (only on non-US market)	None	Psychedelic	Narcotic addiction, unproven
Ibutilide	Corvert®	Antiarrhythmic	Abnormal heart rhythm
Levofloxacin	Levaquin®, Tavanic®	Antibiotic	Bacterial infection
Levomepromazine (methotrimeprazine) only on non-US market)	Nosinan®, Nozinan®, Levoprome®	Antipsychotic	Schizophrenia
Levosulpiride (only on non-US market)	Lesuride®, Levazeo®. Enliva® (with rabeprazole)	Antipsychotic	Schizophrenia
Levomethadyl acetate (removed from market)	Orlaam®	Opioid agonist	Narcotic dependence
Mesoridazine (removed from market)	Serentil®	Antipsychotic	Schizophrenia
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadon®	Opioid agonist	Narcotic dependence, pain

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Moxifloxacin	Avelox®, Avalox®, Avelon®	Antibiotic	Bacterial infection
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®	Antiemetic	Nausea, vomiting
Oxaliplatin	Eloxatin®	Antineoplastic Agent	Cancer
Papaverine HCl	none	Vasodilator, Coronary	Diagnostic adjunct
Pentamidine	Pentam®	Antifungal	Fungal infection (Pneumocystis pneumonia)
Pimozide	Orap®	Antipsychotic	Tourette's Disorder
Probucol (removed from market)	Lorelco®	Antilipemic	Hypercholesterolemia
Procainamide	Pronestyl®, Procan®	Antiarrhythmic	Abnormal heart rhythm
Propofol	Diprivan®, Propoven®	Anesthetic, general	Anesthesia
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®	Antiarrhythmic	Abnormal heart rhythm
Roxithromycin (only on non-US market)	Rulide®, Xthrocin®, Roxl-150®, Roxo®, Surlid®, Rulide®, Biaxsig®, Roxar®, Roximycinv®, Roxomycin®, Rulid®, Tirabicin®, Coroxin®	Antibiotic	Bacterial infection
Sevoflurane	Ulane®, Sojourn®	Anesthetic, general	Anesthesia
Sotalol	Betapace®, Sotalex®, Sotacor®	Antiarrhythmic	Abnormal heart rhythm
Sparfloxacin (removed from market)	Zagam®	Antibiotic	Bacterial infection
Sulpiride (only on non-US market)	Dogmatil®, Dolmatil®, Eglonyl®, Espiride®, Modal®, Sulpor®	Antipsychotic, atypical	Schizophrenia
Sultopride (only on non-US market)	Barnetil®, Barnotil®, Topral®	Antipsychotic, atypical	Schizophrenia
Terfenadine (removed from market)	Seldane®	Antihistamine	Allergic rhinitis
Terlipressin (only on non-US market)	Teripress®, Glypressin®, Terlipin®, Remestyp®, Tresil®, Teriss®, and others	Vasoconstrictor	Septic shock
Terodiline (only on non-US market)	Micturin®, Mictrol® (not bethanechol)	Muscle relaxant	Bladder spasm

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Thioridazine	Mellaril®, Novoridazine®, Thioril®	Antipsychotic	Schizophrenia
Vandetanib	Caprelsa®	Anticancer	Cancer (thyroid)

Note: Includes those drugs known to prolong the cardiac QT interval or cause TdP (Woosley 2018> 8 days8).

Abbreviation: QT: Time of start of Q wave until end of T wave in the heart's electrical cycle; TdP: Torsades de Pointes; UK: United Kingdom; US: United States

15.3. ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Reference: [Oken 1982]

15.4. Protocol Amendment History

15.4.1. Summary of Changes: Version 2 (10 July 2020)

15.4.1.1. Overall Rationale for the Amendment

This amendment clarifies wording in the 22 June 2020 version of the clinical protocol and addresses requests received from the FDA following FDA review of the 22 June 2020 version of the clinical protocol.

15.4.1.2. 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	To make appropriate editorial modifications
Table 1: Schedule of Activities 3.1 Primary Objective 3.2 Secondary Objectives 4.1 Primary Endpoint 4.2 Secondary Endpoints 4.3 Exploratory Endpoints 5.1 Study Design 5.4 Rationale for Study Design 11 Efficacy Assessments 12 Statistical Considerations	• Timing of sampling were clarified or updated • Assessment of mRNA from nasopharyngeal swab and saliva on Day 28 was added • Cytokine analysis on Day 4 was added • Definition of clinical status endpoint was corrected • Definition of oxygen saturation endpoint was corrected • SARS-CoV-2 viral load endpoints relating to nasopharyngeal and salivary samples were added or clarified • Definition of cytokine endpoint was corrected • Definition of viral genome sequence endpoint was corrected	To ensure consistency of assessment and to address FDA requests
Table 1: Schedule of Activities	• Instructions regarding timing of screening ECG, hematology testing, and serum chemistry testing were modified	To define allowable screening window for these tests
Table 1: Schedule of Activities	• Requirements for fasting during pharmacokinetic assessments were included	To ensure consistency of fed-fasting status during pharmacokinetic evaluations
6.1 Inclusion Criteria	• Modified definition of symptoms of mild COVID-19 disease	To provide clarification
Table 1: Schedule of Activities 8.1. Supportive Care	• Discussion of use of illicit drugs removed	To delete unneeded text
9.1.2 Serious Adverse Event	• Text was modified to indicate that deaths due to COVID-19 (rather than cancer progression) may be defined as SAEs	To correct SAE definition

Section or Table Number	Description of Change	Brief Rationale
9.7.2 Pregnancy	• Reporting requirements for pregnancy in female partners of male subjects were updated	To ensure timely reporting of such occurrences
12.4.5 Exploratory Endpoints	• Erroneous reference to exploratory objectives was removed and analyses were referenced to the SAP or separate reports	To clarify plan for analyses of exploratory endpoints
12.4.10 Other Analyses	• Section was removed	To delete unneeded text
13.11 Study Drug Accountability	• Instructions for recording of bottle numbers were included • Instructions for disposition of study drug were updated	To clarify appropriate procedures for study drug accountability

15.4.2. Summary of Changes: Version 3 (31 August 2020)

15.4.2.1. Overall Rationale for the Amendment

This amendment incorporates the following changes to the protocol.

15.4.2.2. 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 • Changes in the synopsis were made consistent with changes to the body of the protocol document	To make appropriate editorial modifications
Table 1: Schedule of Activities	• Instructions were included to described activities to be performed in a subject terminating from the study prematurely • The timing of the LAM-002A compliance checks was clarified • Incorrect mention of urinalysis was removed from the table • It was indicated that screening and baseline visits could occur on the same day. • Instructions for drug dispensing were clarified • It was indicated that subjects taking only a single dose of study drug on Day 1 due to initiation late in the day should continue drug through Day 11 in order to ensure completion of a full 20 doses of study drug administration. • It was indicated that compliance would be assessed at each visit throughout the dosing period. • To enhance flexibility in study conduct, it was noted that obtaining nasopharyngeal swabs on Days 6 and 8 would be optional; saliva would still be collected at these time points, thus allowing an alternative and better tolerated evaluation of viral load	To provide appropriate direction to investigational personnel
2.1 Study Rationale 5.1 Study Design 6.1 Inclusion Criteria (Number 4)	• The permissible duration of COVID-19 symptoms before study enrollment was increased from 4 days to 8 days	To permit greater flexibility in prestudy symptom duration to enhance ease of subject enrollment.

Section or Table Number	Description of Change	Brief Rationale
3 Study Objectives 4 Study Endpoints 5.Study Design 11 Efficacy Assessments 12 Statistical Considerations	• Multiple sections of the protocol were modified to indicate that that the study would focus on analyzing subjects with a baseline viral load of $>10^5$ copies/mL; accordingly, the total sample size was increased to ~284 subjects to ensure accrual of the sample of ~142 subjects with baseline viral load of $>10^5$ copies/mL required to perform the analysis consistent with the primary hypothesis of the study • An antiviral efficacy analysis population consisting of all randomized subjects with a baseline viral load $>10^5$ copies/mL was added • Clarifications were provided regarding the populations (ITT, Antiviral Efficacy, PP) to be analyzed for each endpoint	To ensure that there would be sufficient subjects with an adequate viral load to allow evaluation of LAM-002A effects and to update and clarify the populations in which specific analyses would be performed
6.1 Inclusion Criteria (Number 3)	• The types and specificity of the descriptions of permissible symptoms of COVID-19 necessary for study enrollment was enhanced	To improve clarity and enhance enrollment potential
8.2.3 Dose Schedule Interruptions and Vomited Doses	• It was indicated that subjects taking only a single dose of study drug on Day 1 due to initiation late in the day could skip taking a 2^{nd} dose on that day, could resume study drug administration on the morning of Day 2 and continue drug through Day 11 in order to ensure completion of a full 20 doses of study drug administration.	To provide clarification to study center personnel and study subjects regarding permitted variations in the dosing schedule
12.4.7 Plan for Missing Data	• The reasons for not considering a subject for analysis were updated to include a false positive test for SARS-CoV-2 (in additional to withdrawal of consent or lost to follow-up).	To clarify the analysis plan
14 Bibliography	• An explanatory reference was added	To document the approach to logistic regression analysis

15.4.3. Summary of Changes: Version 4 (16 October 2020)

15.4.3.1. Overall Rationale for the Amendment

This amendment incorporates the following changes to the protocol.

15.4.3.2. 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. • Changes in the synopsis were made consistent with changes to the body of the protocol document.	To make appropriate editorial modifications
Table 1: Schedule of Activities	• Day 6 and 8 were changed to remote visits. • Footnote d of the Schedule of Activities was added to clarify an optional provision for a confirmatory viral test for those who do not have a documentation of a positive test. • Vital signs/oxygen saturation on Days 6 and Days 8 were removed in Footnote i. • Telehealth visits on Days, 6, 8 and 22 were noted in the Schedule of Activities table header. • Footnote j was clarified to indicate that the AE review on Days 6, 8 and 22 will be via telehealth/telephone. • Footnote k was changed to indicate that the concomitant medication review on Days, 6, 8 and 22 will be via telehealth/telephone. • Footnote r was added regarding subject COVID-19 symptoms diary . • Footnote v was added for saliva sample collection on Days 1, 4, 11, and 28.	To provide appropriate direction to investigational personnel
Section 1: Protocol synopsis	• The secondary objective for antiviral assessment from nasopharyngeal samples on Days 11 and 28 were removed. • The secondary objective for assessment of O_2 saturation was changed from Days 1, 4, 6, 8 and 11 to Days 1, 4, and 11. • The exploratory objective for antiviral assessment was hanged from nasopharyngeal samples on Day 6 to saliva samples on Day 4. • The exploratory objective for antiviral assessment using nasopharyngeal samples on Day 8 was changed to saliva samples on Day 11.	To provide appropriate direction to investigational personnel. To clarifies timing of antiviral assessments and the type of sample (whether nasopharyngeal vs saliva). To add an alternative nasopharyngeal endpoint.

Section or Table Number	Description of Change	Brief Rationale
	• A separate exploratory objective for saliva antiviral assessment was specified at Day 28. • An antiviral assessment in saliva samples based on AUC analysis added • An exploratory anti-viral assessment was added based on the difference in the proportion of subjects with SARS-CoV-2 viral load <LLOQ between the LAM-002A and the placebo as measured by a qRT-PCR test from nasopharyngeal samples at Day 4. • A requirement was added for written documentation of SARS-CoV-2 infection via a validated test.	
Section 3: Study Objectives	• Secondary and exploratory objectives were revised to align to objectives in synopsis (Section 1)	To align study objectives with those in the synopsis
Section 4: Study Endpoints	• Primary endpoint: Added clarifying language around quantitation of viral load • Secondary Endpoint for antiviral assessment from nasopharyngeal samples on Days 11 and 28, and by AUC analysis was removed • Secondary Endpoint for assessment of O_2 saturation was changed from Days 1, 4, 6, 8 and 11 to Days 1, 4, and 11. • Exploratory endpoints for assessment of viral load from nasopharyngeal samples at Day 6 and Day 8 were removed. • The endpoint of difference in proportion of subjects with SARS-CoV-2 viral load <LLOQ between the LAM-002A and the placebo as measured by a qRT-PCR test from nasopharyngeal samples at Day 4 arm was added.	To clarify changes in study endpoints and add an alternative exploratory endpoint
Section 5.1 Study Design	• Paragraph 1: Text was added regarding asymptomatic subjects with a positive test. • Paragraph 2: Information was added regarding randomization via a centralized randomization system. • Paragraph 2: Stratification by site was removed.	To allow flexibility in randomization
Section 5.2 Study Conduct	• Paragraph 3: It was clarified that a CRO other than Yale University could become involved in conduct of the study.	To permit alternatives approaches to operational coordination
Section 6.1 Inclusion Criteria	• The need for written documentation of a positive test was included.	To include more outpatients and document positive infection.

Section or Table Number	Description of Change	Brief Rationale
	• Text was added to allow for inclusion of asymptomatic patients.	
Section 7.1 Randomization	• Text was added to accommodate more clinical sites.	To provide additional operational flexibility
Section 8.1.4 Shipping Storage and Stability	• Paragraph 2: Reference to Yale University was replaced with more general language to add operational flexibility	To clarify change in operational coordination
Section 9.7.3	• Management of contact information for SAEs and pregnancy was changed from Yale University to a CRO	To clarify change in operational coordination
Section 10.1 Laboratory and Other Parameters to be Assessed	• A footnote was added to Table 6 (Laboratory and Other Parameters to be Assessed), clarifying that samples for these exploratory endpoints will be collected but analysis of the samples is optional	To provide clarity to investigation personnel
Section 10.1 Methods and Analytes	• Paragraphs were added to clarify method of viral load measurements and limits of detection (LLOQ), details of pharmacodynamic and biomarker measurements, and optional nature of some assays	To provide clarity to investigation personnel
Section 11.1	• Additional text was added to define the analysis of primary endpoint	To provide clarity on endpoint
Section 12 Statistical Considerations	• Paragraph 2: stratification by site was removed. • Changes in statistical parameters were incorporated.	To clarify stratification and adjust statistical analysis
Section 12.4.4 Analysis of Secondary Outcomes	• The secondary endpoint for analysis of nasopharyngeal viral load analysis at Day 11 and by $AUC_{Day1\text{-}Day11}$ was removed. • It was specified that analyses of secondary endpoints will be in the antiviral efficacy analysis population (population with viral load $>10^5$ copies/mL).	To provide clarity to investigation personnel To clarify the statistical analysis population for secondary endpoints
Section 12.5 Interim Analyses	• Potential DSMB decisions regarding interim analyses were updated.	To clarify statistical analysis population for interim analysis.
Section 14 Bibliography	• The Carpenter et al. reference was added.	To provide support for the statistical approach.